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A BRIEF COMPARISON OF TUBERCULOSIS IN THE WHITE, INDIAN AND NEGRO RACES[1]

ESMOND R. LONG[2]

A comparison of tuberculosis in different races inevitably raises the question of innate differences in susceptibility and resistance. However, intrinsic variations are exceedingly difficult to evaluate, because they are obscured by obvious complicated and inconstant environmental differences. Economic status, hygienic standards, housing and dietary customs are of universally recognized importance in determining the course of tuberculosis. In general, the white race has the advantage over the other two races named in all these respects. How important this fact is in determining its apparently greater resistance to tuberculosis must be decided on the basis of facts available. The present period may be looked upon as one of fact-finding, and in this paper what appear to me to be important simple facts will be briefly assembled.

There is an unmistakeable and wide variation in the tuberculosis mortality of the three races. The average death-rate for whites throughout the country is about 57 per 100,000, and while the extremes, as determined by occupation and economic status, vary considerably from this figure, the highest figure is but slightly above the average figure for tuberculosis mortality in Negroes. The average for Negroes is three to four times the average for whites, again with noteworthy variations in different occupations, and in different regions. The average figure for Indians is not known, but the few studies on record indicate that in certain localities it must, in turn, be three or four times as high as the tuberculosis death rate for Negroes. Rates varying from 1,327 per 100,000 in Montana (Crouch) to 220 per 100,000 in New York (Korns) are recorded. It may well be that the figures obtained in the years to come, from different tribes in the East, West, North and South, will show a greater variation in tuberculosis mortality among the Indians than in the other two races. Because of different local conditions reservation

[1] Presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936.

[2] The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

returns on Indian tuberculosis mortality at present are highly incomplete. Indeed, one of the most important needs of the Indian Service is the development of a census program, accurately recording, among other things, the tuberculosis deaths, so that the success of present and future methods of control can be evaluated.

It should be noted in this connection that, among Indians, a definite correlation exists between the tuberculosis mortality and the degree of intermixture with white blood. Ferguson in Alberta, Crouch in Montana, Walton in Manitoba, and others have presented figures indicating a much higher rate in full-blood Indians than in Indian-white mixtures, and a higher rate in both than in whites of the same community. Naturally this again raises the question of inherent racial susceptibility, but it must not be forgotten that, with variation in degree of Indian blood, there is a corresponding variation in hygiene and habits. The problem is difficult, and much further study is needed to appraise the various factors in the high Indian mortality rate.

The figures for morbidity in all groups are still less trustworthy, because the reporting of cases is highly faulty. In the first place, there is no general agreement as to what constitutes a case of tuberculosis, and, second, what is obviously active tuberculosis is commonly brought to medical attention for the first time long after its inception. As a general rule, it may be stated that, the more chronic the course of the disease, the larger the number of active cases in proportion to the number of deaths. Chronicity swells the morbidity lists both through the accumulation of long-lived patients, ultimately dying of other cause, and the continued widespread distribution of tubercle bacilli.

In this connection the figures of Opie and McPhedran are of special interest. Opie compared the duration of illness from tuberculosis in white patients attending the dispensary of the Henry Phipps Institute in Philadelphia with the duration in Negroes attending a similar clinic in Kingston, Jamaica. The length of the disease in the whites was approximately three times that noted in the Negroes. In a later paper on the spread of tuberculosis in Negro families, McPhedran and Opie have called attention to the rapid character of the preliminary disease in some families, the whole course from onset to fatal termination sometimes lasting only four months, and several members of a family passing from health to fatal issue within the period of a year.

Figures such as those from Framingham and Cattaraugus County set useful standards for morbidity in stabilized communities of white peo-

ple, but these figures probably do not hold for communities where the disease is more acute and of shorter duration, as may be the case with both the colored races. It is important that we gather more data on the spread of tuberculosis in Negro and Indian groups and establish standards on the ratio of infection, morbidity and mortality. It seems probable that the Framingham standards will not apply to Negroes, but they might be useful in estimating the morbidity in certain groups of Indians, if, as the present limited investigations suggest, the chronicity of the disease in whites and Indians is similar. However, the wide divergence of living conditions among different tribes makes the application of any standard hazardous.

The figures for infection-rate, as determined by numerous recent tuberculin surveys, are highly illuminating. We now have adequate data from widely separated communities on the incidence of positive tuberculin reactions by age-groups in the white, Negro and Indian races. It will be recalled that the rapid course and high fatality of tuberculosis in the Negro were at one time explained on the ground that Negro tuberculosis was essentially first-infection tuberculosis of rapidly progressive type, occurring in adult years, because of the general failure of Negroes from the rural districts to receive in childhood the mild immunizing infections believed to be the rule in white children. While childhood-type tuberculosis may occur in adult Negroes, this concept as a general explanation of the severity of Negro tuberculosis now appears quite erroneous. Large surveys have repeatedly shown that Negroes in various parts of the country, both in rural and urban districts, are likely to present a higher and more rapidly rising infection rate in the early years of life than whites. Moreover X-ray study and pathological examination commonly show encapsulated and calcified nodules of first infection in Negroes dying of pulmonary tuberculosis in adult years, just as they do in whites. The different anatomical character of Negro tuberculosis, and its more fulminant course, must therefore be sought on other grounds.

That Indians, also, are heavily infected in the childhood years, and apt to surpass whites of the same community in the early acquisition of childhood-type infections, has been repeatedly demonstrated. As Ferguson said years ago, the Indians of the Great Plains are thoroughly tuberculized. Recent studies in Canada, Montana, New York, and other states regularly show a higher incidence of positive tuberculin reactions in Indian school-children than white children in the same

schools. That Indians display good resistance to these childhood primary infections is also shown by the X-ray finding of approximately as many calcified nodules and nodes in the chests of Indian children as whites in the same locality. Therefore, among Indians also, the high mortality rate is not to be attributed to lack of immunizing first infection and the adult advent of progressive first infection disease.

It would be superfluous to call attention to the anatomical and clinical charactersitics of tuberculosis as commonly seen in the white race, but it seems in order briefly to review here what is known of the tuberculosis of the other two groups.

The tuberculosis of the Negro, as compared with the average in the white is generally more massive in character, with more tendency to caseous pneumonia, and to generalization by both blood- and lymph-streams, with resultant wider variation in anatomical type. Clinically, it is characterized commonly, as we have seen, by a more acute course and shorter duration. However, the utmost chronicity of the disease is often seen in the Negro. Necropsy experience frequently shows a preponderance of the chronic types. This is the case at the Henry Phipps Institute. The impression in the Clinic, based on the average course of the disease and the usual roentgenographic appearance, is of a disease of subacute course, but in half of the necropsies secured in the hospitals with which we have affiliations the disease is seen to be highly chronic. We attribute this difference to the selection obviously involved in obtaining permission for postmortem examination.

The tuberculosis of the Indian, contrary to the general impression, is, in our experience, of relatively chronic character, and more like that seen in the white than that commonly observed in the Negro. Our experience is limited to the tribes in the Southwest. It is in agreement, however, with the experience of Korns in as distant a region as the Allegany Reservation in New York. Our impression is based entirely on X-ray observation and clinical course of the disease. So little necropsy experience has been recorded that statements on anatomical type, except on an X-ray basis, cannot be made with conviction. From X-ray study, however, it can be said that childhood-type infection is common, with obvious tendency to healing, and that the course of the adult-type disease is protracted, with the usual roentgenographic appearance of marked chronicity in the pulmonary form. Nonpulmonary forms, while seen in the group we have studied, are by no means as common as recorded for the Indians of a generation ago. Patients found with advanced tuberculosis in a survey made a year ago are still in sanatoria,

either improved or little changed in condition. A distinct difference from tuberculosis among whites, however, is seen in the more frequent occurrence of the adult type of tuberculosis in the age-period from 11 to 13 years. As is well known, Negroes exhibit the same difference as compared with whites.

Among these Indians economic conditions and hygienic standards are low. Housing is such as to lead to overcrowding and intense exposure to infection. Hence the high infection rates, as determined by tuberculin testing, are easily understood. So, likewise, is the high mortality rate, if we accept the theory of exogenous adult-type infection. But the chronicity of the disease, in spite of such conditions, is notable, and should be an encouraging element in the formulation of adequate plans for control.

In the evaluation of factors responsible for racial peculiarities in tuberculosis it is just as important to learn those responsible for chronicity of disease as those making for the more spectacular fulminant course. We not infrequently see examples of tuberculosis in the Negro of more prolonged course and favorable trend than are seen in the majority of whites with this disease, in spite of environmental influences that would seem highly unfavorable. It would be worth while, if possible, to learn the genetic background of such individuals as compared with their more susceptible fellows. Racial stocks in this country have passed through varying periods of survival of the most fit. Some stocks have more than three centuries of contact with tuberculosis behind them, and others scarcely one. It may well be assumed that constitutional factors are involved and that natural selection could have considerable effect in raising the level of native resistance in the course of three centuries, and that such an effect would be much greater in three centuries than one.

So also with Indians. There is reason to believe that different tribes have known tuberculosis different lengths of time, and some of them a very long time, and that natural selection of the most fit, as far as tuberculosis is concerned, has been at play long enough in some groups to select a group of high resistance, even where environmental factors make for widespread disease.

Without minimization of the obvious importance of evaluating environmental factors it is probable that anthropological and historical studies on the development of our racial stocks in this country may still shed considerable light on the problem of racial variability in response to infection with tuberculosis.

RACIAL ASPECTS OF TUBERCULOSIS IN MEXICO[1]

DONATO G. ALARCÓN[2]

Since I first came to this Country I have been frequently asked by medical men whether I had observed some special features of tuberculosis in Mexico that might be attributable to ethnological factors.

I have devoted some attention to this problem, studying it in Mexico and among the Mexican population of the United States.

This paper discusses the matter of the susceptibility of Mexicans to tuberculosis, denying it from the racial standpoint. Some other causes are claimed to be responsible for the relatively high mortality in some localities and among some groups.

According to the Census of 1930, the population of Mexico was then 16,553,000 inhabitants, but it is very difficult to determine exactly which proportion belongs to the different races living in our Country.

However, it is known that the white race is represented by 1,500,000 people. The Census of 1930 does not pretend to discriminate racial proportions, inasmuch as the race to which each individual pretends to belong is frequently false.

On the other hand, if we consider just the dialect-speaking people, we get a very low proportion of Indians, as the number of Indians who have left or even never did speak the native dialect is increasing.

The Census of 1930 tells us that there are 12,835,000 Spanish-speaking people and only 2,251,000 dialect-speaking in Mexico.

Considering that the estimated increase of population from 1921 to 1930 was 2,000,000 and distributing proportionally this number among the races, we might say that in 1930 there were about 1,500,000 white people, 5,000,000 Indians and 10,000,000 of mixed Spanish-Indian extraction.

As for the Negroes, we might say that there are only small groups of this race which are not important in the racial character of Mexico.

[1] Presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936.

[2] Medical Director of the Tuberculosis Sanatorium of the Public Welfare of Mexico, Mexico City.

This assertion is against those of Drolet and others, who stated that the Mexican population is formed by a mixture of whites, Indians and Negroes.

Tuberculosis mortality is particularly high among mixed-blood people on account of their great number and because this group constitutes almost exclusively the great industrial centres.

Pure Indians, dialect-speaking, live in small isolated communities, their work being agricultural or some small crafts that we might call household industries.

Their real isolation can be estimated by the fact that they speak a native dialect and the intercommunication among tribes is very limited, for there are 52 different dialects in Mexico.

Some few Indians live in the cities, speak Spanish, take advantage of the civilized modern life, and go hand-in-hand with the other groups. Their contact with the other people is perfectly free.

Among these people we have had the opportunity to study the anatomicoclinical types of pulmonary tuberculosis, and on this experience the statements held in this paper are based.

For the identification of pure Indians, Spanish-speaking and living like mestizos, we have only the racial features as a guide, such as shape of body and face, color, pigmentation, hair-distribution, and particularly a knowledge about their parents and relatives. It is therefore difficult to classify them with certainty.

The pure Indians might be easily found in numbers among the dialect-speaking people, but they live isolated and far from daily contact with the infectious white or mestizo. What we need is to study the reactions of the Indian in contact with these white and mixed people in the cities where tuberculosis develops easily.

Is tuberculosis more frequent among Indians than among white people? It is difficult to answer this question. The proportion, Indian-mestizo-white, is not easy to determine, because there are no accurate statistical studies available in the cities.

Common medical practice cannot give an idea of morbidity.

Patients attend the clinics in proportion to their culture. Mestizos are by far more numerous at the clinics.

Revising my files from private, dispensary and hospital practice which together involve about a thousand cases in the last five years, I find that the attending patients were 5 per cent whites, 80 per cent mixed, and 15 per cent pure Indians. Of course, we cannot rely upon these numbers to determine the incidence of tuberculosis in a given group.

But, even if tuberculosis were more frequent among Indians, this higher frequency could be easily explained by the way they usually live,—doing the hardest work, earning the lower wages and living in the poorest houses; all of which might explain a higher morbidity if it were proved, which is not the case.

Do pure Indians present a more rapidly fatal type of tuberculosis, or is there a deficient response or special susceptibility to the disease among them?

The greater susceptibility of a group can be estimated by the following characteristics: (1) greater frequency of progressive types of pulmonary tuberculosis as compared with other racial groups; (2) shorter time of course between incipiency and death; (3) lower proportion of arrested disease among subjects under the same circumstances; (4) predominance of caseoexudative lesions over fibrous lesions comparatively with the other groups, and higher frequency of exudative and haematogeneous spreading; and (5) deficient immediate response to modern means of treatment.

We are unable to answer the first question, as already explained. With reference to the second point, this is very hard to estimate, the influence of early diagnosis and early treatment on the duration of the disease being known.

As a matter of fact, the great majority of cases we see come to us in the far-advanced stage. My records show that 10 per cent were incipient, 20 per cent moderately advanced, and 70 per cent far advanced when first seen.

Our people ignore their disease at its onset. They attend the clinics when forced by extreme poverty or when unable to work any more. I am used to seeing two predominant groups of patients calling on the clinics,—the far-advanced, almost unable to stand up, and the patient alarmed by haemoptysis. Practically all patients not calling following their first haemoptysis were cases of more than one-year duration. Only 20 per cent were haemoptysis cases. The others react poorly to treatment, as long-standing cases usually do.

On the other hand, we have to consider our deficiencies for the institutional care of tuberculosis. We have only recently opened our first public sanatorium and prior to this we had only the beds of the general hospitals. However, we do not find a deficient organic response among our patients compared with that seen among other people in other countries.

The proportion of haematogenous and exudative types compared with that of localized fibrocaseous cases of definite character, according to our statistics, is as follows: haematogenous types, 2 per cent; predominantly exudative without fibrous reaction, 5 per cent; and localized and extensive fibrocaseous as well as predominantly fibrous, 93 per cent. The immediate response toward modern means of treatment is about the same in the three racial groups. We do not find that race has any influence in the immediate results of artificial pneumothorax or other surgical procedures or in hygienic-dietetic treatment. Under the same economic conditions, in the same stages, in the same phases of evolution, all patients react equally, regardless of the race to which they belong.

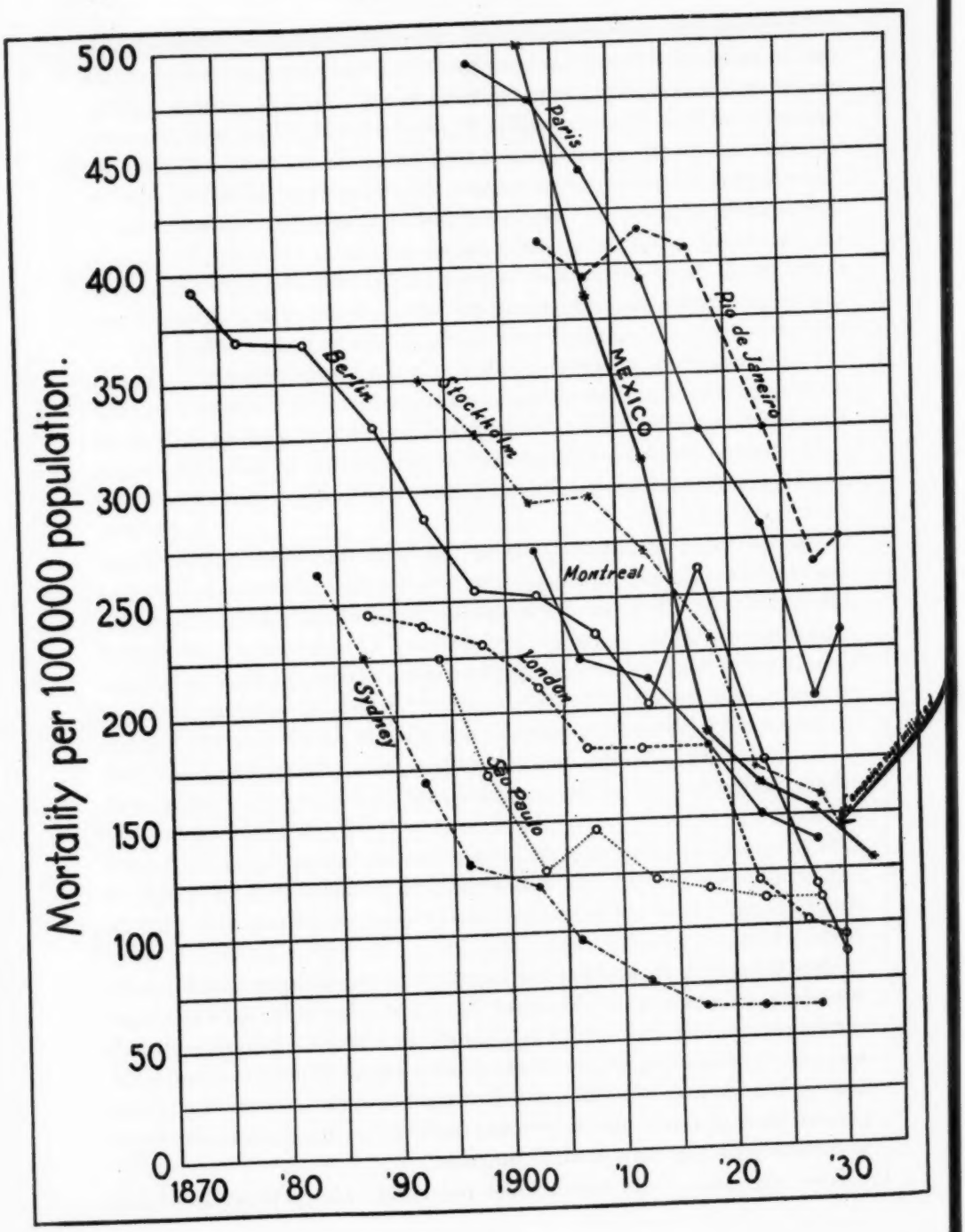
The tuberculosis mortality in Mexico is not much higher than that of the United States, and according to certain statistics it is lower. In 1930 I undertook a study of this subject, and found a death-rate of 69 from tuberculosis. But also I demonstrated that certain localities of Mexico on the Gulf Coast are terribly afflicted, while others give the lowest figures in the World.

The mortality of Mexico City is the most interesting instance and deserves special consideration. The death-rate from tuberculosis was 500 in 1900; from that year it fell rapidly, reaching 130 in 1930. This is an exceedingly interesting fact. The decrease of tuberculosis in Mexico City is not a result of a campaign by such well-known measures as dispensaries, sanatoria, education, etc., but probably the result of a general improvement in living conditions among laborers as a consequence of the social movement of Mexico and its resulting march toward progress which allows better houses, accommodations, etc., for the greater number of citizens.

We are far from denying the importance of the campaign as carried out in other countries. We believe that if we had had a campaign of this kind we could have reached now a mortality lower than 130 in Mexico City.

Here is a graph taken from the League of Nations, upon which I have superimposed our graph of Mexico City. The other cities were waging a campaign; our city was not. On account of its internal troubles, Mexico had had to endure pandemic tuberculosis without a special organization against the disease. In 1929, our Government undertook the campaign; and we hope to accelerate the descent of the tuberculosis mortality more and more with the help of this campaign.

Here are some facts worth-while reflecting: The population of the


Mortality per 100000 population.
500
450
400
350
300
250
200
150
100
50
0
1870
'80
'90
1900
'10
'20
'30
Paris
Berlin
Stockholm
MEXICO
Rio de Janeiro
Montreal
London
Sydney
São Paulo

United States is eight times greater than that of Mexico. The actual deaths from tuberculosis are about eight times greater in the United States: those of Mexico being 11,000, and of the United States 85,000; and yet we have less than one-tenth the beds available for tuberculosis in Mexico in relative numbers, and only about one-eighty-fifth in absolute numbers.

However, our problem is real, because we have some localities with a very alarming mortality, as, for instance, Tampico and Vera Cruz, where the mortality has surpassed the rate of 400 in some years.

Considering the most populated centres of Mexico, we find that mortality is certainly higher than that of the American cities. Studying the causes other than the racial which we have discarded, I found more interesting facts, to which I want to attract your attention.

One of the most interesting is the plurinatality in Mexico. According to the United States Census in 1930 and that of Mexico of the same year, the population under ten years of age in Mexico was 25.90 per cent and that of the United States was 19.60 per cent of the total. Data from the same sources reveal that the American family is composed of approximately four individuals, while the Mexican family consists of five. For the estimation of the real natality of Mexico, which is far higher, there are not available numbers, but we might recall that infantile mortality is enormously high, and yet we have a difference of one member more per family.

From the former data we can say that, given a case of infectious tuberculosis, the contacts in Mexico should be four while in the United States they should be three; and, unless we deny the importance of the number of contacts in the spreading of tuberculosis, we have to admit that plurinatality is an important fact in morbidity and mortality from tuberculosis.

It is a fact that the American family is decreasing its number of members. This is common to the more cultured countries; and the result is that children have better care and education and are more economically protected from disease. Mortality decreases among children, but the population does not increase as was expected. While the United States have a population eight times greater than that of Mexico, its children's population is only six times greater.

Now let us consider the tuberculous mortality among Mexicans living in the United States.

A few years ago the attention of the American medical public was

attracted by the work of Mendelsohn, Goldberg and others, who concluded that Mexicans presented a racial susceptibility to tuberculosis. My own research on this subject, with which I will not deal extensively in this paper, pointed out the following conclusions:

1: The composition of the population of Mexico was erroneously estimated, following the statements of Drolet and others, who stated that Mexicans are the result of a white-Indian-Negro mixture.
2: The term, *Mexican*, is not a racial denomination but that of a nationality whose principal racial groups are white, Indian and mestizo of Spanish-Indian extraction.
3: The greater frequency of tuberculosis among Mexicans living in the United States is due to (1) the poverty of Mexican immigrants, bad housing, unbalanced diet and resulting poor hygiene, and (2) dangerous occupations afforded them (foundries, stockyards, contracts allowing child-labor, etc.).

Now we have to add the plurinatality already mentioned as a factor.

We may recall the important research of Emil Bogen in California, pointing out that Mexicans, compared with other races, do not present any susceptibility or deficient response to treatment attributable to their racial characteristics, and that, as a whole, they react to institutional treatment in the same way as do other races, provided the circumstances of duration of illness, time of treatment, etc., are equal.

Let us also mention Long's paper on tuberculosis among the Papago Indians, who belong to the Pima stock to which several tribes of northern Mexico belong. According to Long's work, tuberculosis among the Papagos does not appear with any specially malignant character from the pathological standpoint. He, as myself, found the same types, predominantly the chronic fibrous form, among those Indians and not the predominantly caseoexudative almost without fibrous reactions seen in other races.

Undoubtedly there is a vast field deserving investigation, and further studies should come to confirm our views. The result of my personal study of the problem and of my clinical experience among my countrymen and among other people is presented.

In conclusion, it should be admitted that, by their racial characteristics alone, the Indians do not constitute a race predisposed to tuberculosis.

TUBERCULOSIS IN PUERTO RICO[1,2]

J. RODRIGUEZ PASTOR

MORTALITY

Tuberculosis is the first cause of death in Puerto Rico, having been responsible for 14.4 per cent of all the deaths occurring on the island during the period 1931–1935. The average death-rate for these five years was 304 deaths per 100,000 population, or about five times the United States average for the same period of time.

TABLE 1

Deaths from tuberculosis in Puerto Rico

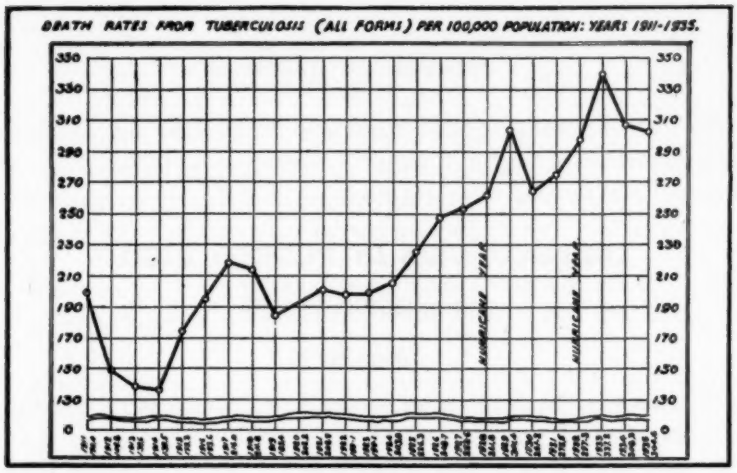
YEAR	TOTAL DEATHS	DEATHS FROM TUBERCULOSIS	PER CENT OF TOTAL
1931	32,146	4,338	13.5
1932	35,610	4,755	13.4
1933	36,763	5,476	14.9
1934	31,703	5,082	16.0
1935	30,753	5,096	16.6

The tuberculosis mortality (1932–1934) is 16 per cent higher in women than in men, and reaches its peak for both sexes in the age-period 25–29. In both sexes the mortality is comparatively low until the age-period, 10–14, when it begins an abrupt rise which is more notable in women than in men. During the age-period, 25–29, the mortality curve comes down in both sexes and keeps coming down steadily in women; but in men it begins to rise again in the next age-period (30–34) becoming higher than in women after 45, and reaching a second peak in the age-group 65–74 (graph 3). The mortality is 13 per cent higher in the colored race than in the white.

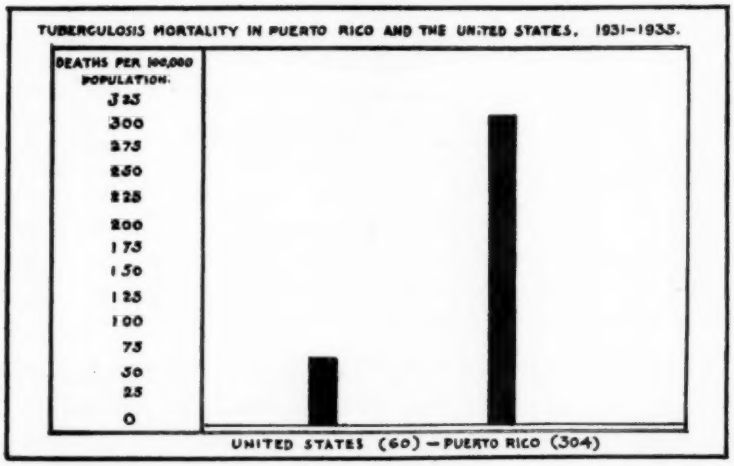
Recent surveys have shown that the incidence of manifest tuberculosis in the general population is 2.4 per cent in the coastal towns and 1.1 per

[1] Presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936.

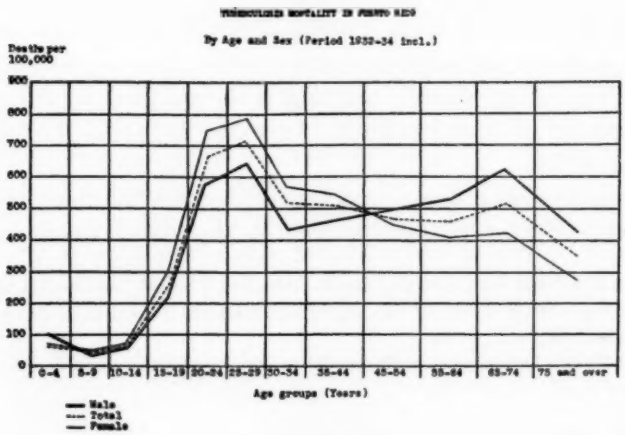
[2] From the Health Department of Puerto Rico, San Juan, Puerto Rico.



Graph 1



Graph 2

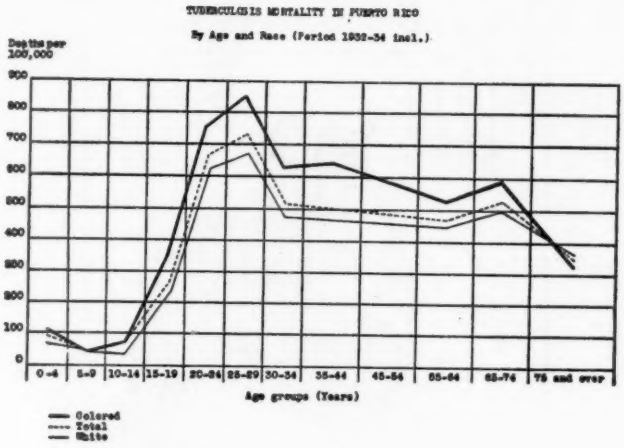


Graph 3

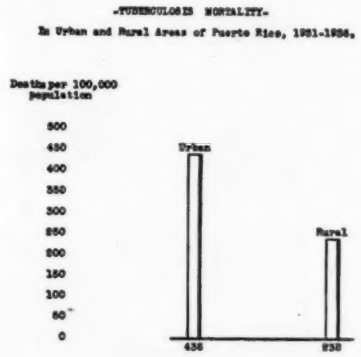
PLATE 1

cent in the mountains of the interior. Pulmonary tuberculosis is responsible for 96 per cent of all the deaths from the disease.

The high tuberculosis mortality in Puerto Rico is due, first, to the extreme poverty of a large proportion of the inhabitants, and to the overcrowded conditions in which they live. Every town has its slums,



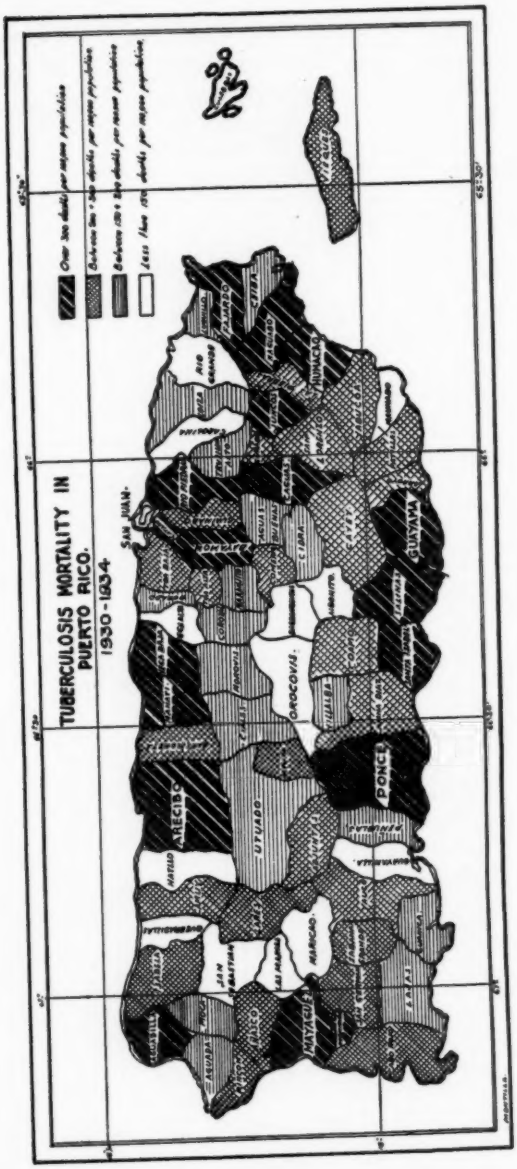
Graph 4



Graph 5

PLATE 2

with numerous tenements where the opportunities for contagion are plentiful. In a recent survey of a San Juan slum, the average number of persons per room was four, and it is not unusual to find as many as ten people living in one small room. The importance of overcrowding as an environmental factor contributing to the seriousness of the disease


TUBERCULOSIS MORTALITY IN PUERTO RICO.
1930 - 1934
SAN JUAN
ARECIBO
UTUADO
PONCE
GUAYAMA
CAGUAS
AGUADILLA
MAYAGUEZ
VIEQUES

is shown by the fact that the urban mortality is 83 per cent higher than the rural.

Hurricanes have helped in the rise of the tuberculosis mortality curve during the last few years. The enormous destruction of dwellings caused by the hurricanes increases the overcrowding and brings about greater opportunities for contagion, especially among the poorest classes.

The increase of tuberculosis mortality in Puerto Rico during the past few years can also be ascribed in part to the very intense case-finding campaign which the Health Department has been carrying out lately. The intensity of this campaign can be judged from the fact that the number of sputum examinations done at the Biological Laboratory of the Health Department increased from 6,557 in 1929–1930 to 24,524 in 1934–1935. Of the latter number, 29 per cent were positive.

In the city of New York, tuberculosis among the Puerto Rican residents is also a serious problem. During the two-year period 1931–1932, when there were 45,000 Puerto Ricans living in New York City, the tuberculosis death-rate among them was 434 per 100,000 population, or over six times the tuberculosis death-rate of the city.

FORMS OF THE DISEASE

These high figures and more or less haphazard observations on a limited number of cases of tuberculosis among Puerto Ricans residing in New York have caused many American observers to conceive the Puerto Ricans as a race of people with a rather low resistance to tuberculosis, comparable, in their reaction to this disease, to the more primitive races, such as the African Negro, or the Indian.

In the 1935 edition of *Diagnostic Standards*, a publication of the National Tuberculosis Association (1), one finds the following statement: "The childhood type of tuberculosis is usually found in children but is not uncommon in adult Negroes, Mexicans, American Indians, Puerto Ricans and Filipinos. It infrequently occurs in white adults."

This same publication, *Diagnostic Standards*, 1935, gives the following definition for the childhood type of tuberculosis: "The childhood type of tuberculosis is the name adopted by the National Tuberculosis Association to describe the lesions in the lungs and associated bronchopulmonary, tracheobronchial and other mediastinal lymph nodes that result from a first infection of the pulmonary tissue with the tubercle bacillus."

According to this definition, the childhood type of tuberculosis should occur with greater frequency among adults giving a low percentage of

positive reactions to the tuberculin test, and it should be relatively uncommon among those peoples who react almost universally to the tuberculin test by the time they reach adulthood. The latter is the case among Puerto Ricans. All the tuberculin surveys made in the island prove that the Puerto Ricans are a highly tuberculized people, and that infection with the tubercle bacillus is almost universal among adults. A recent survey among 4,025 urban dwellers gave the following results: 82 per cent reacted to the intracutaneous tuberculin test between the ages of 10 and 14; 90.6 per cent from 15 to 19; 94.5 per cent from 20 to 29; 98.3 per cent from 30 to 40; and 96 per cent over 40 (2).

Surveys in rural communities have also shown extensive tuberculization, although the percentage of reactions is lower than the above.[3]

TABLE 2

Results of the tuberculin test among 4,025 urban dwellers in Puerto Rico

AGE-GROUP	NUMBER TESTED	PER CENT POSITIVE
0–1	109	22
1–4	492	38
5–9	640	66.6
10–14	565	82
15–19	486	90.6
20–29	706	94.5
30–40	430	98.3
Over 40	597	96

Recent surveys with P.P.D. tuberculin have confirmed the accuracy of the above results.

TABLE 3

Results of the intracutaneous tuberculin test with P.P.D. tuberculin among urban dwellers in Puerto Rico

AGE-GROUP	NUMBER TESTED	PER CENT POSITIVE
0–4	128	40.6
5–9	348	71.6
10–14	608	92.6
15–19	314	94.6
20–29	147	98.0
30–39	92	98.9
40 or more	130	96.2

[3] In these surveys, Old Tuberculin, Meister Lucius, was used. The first dose was 0.1 mgm. O. T. and the second 1.0 mgm. Reactions were read according to the scale used at the Henry Phipps Institute, Philadelphia.

We conclude from the above that, if the definition of the childhood type of tuberculosis given in *Diagnostic Standards*, 1935 edition, is correct, this type of tuberculosis must necessarily be uncommon among Puerto Rican adults. The reason for this conclusion has already been stated: if tuberculosis of the childhood type is the result of a primary infection, it surely cannot occur commonly among the adult population of a community where practically all the adults are already infected.

According to *Diagnostic Standards*, in childhood-type tuberculosis "the parenchymal lesion is usually localized in a lower lobe or lower part of an upper lobe;" but a recent study of the X-ray plates of 1,000 Puerto Rican patients showed that the apices were involved in 82 per cent, while lesions involving only the lower lobes were found in not more than 9 per cent (3).

Diagnostic Standards also states that in childhood-type tuberculosis "the associated bronchopulmonary or tracheobronchial lymph nodes are always involved but may not be demonstrable in the living patient."

The first pathological study carried out in Puerto Rico in relation with tuberculosis was done by Alice M. Burke (4) in 1928. She studied and classified the findings in 124 complete autopsies done in general hospitals of Puerto Rico which do not admit open cases of tuberculosis, and compared these with the results of an equal number of autopsies done at the New Haven Hospital, a general hospital affiliated with the Yale Medical School, where open cases of tuberculosis were likewise not admitted.

Besides these complete autopsies, Dr. Burke studied 1,000 miscellaneous surgical specimens. She concludes as follows:

> Autopsy findings in a series of 124 cases in Puerto Rico and an equal number in New Haven, Conn., show no striking differences in the character of the tuberculous lesions encountered. . . . Though the series of cases is small, we believe the numbers are sufficient to show that the character of the tuberculosis present in Puerto Rico is much the same as in continental United States, indicating therefore, a large measure of tuberculization of the people. This was to have been expected, in view of the long history of close relations between the island and Europe and the North American mainland.

Koppisch (5) has recently made a pathological study on 628 complete and consecutive autopsies on Puerto Ricans, of which 361 were on whites, 175 on mulattoes and 65 on Negroes. He found that "the general incidence of the disease, the incidence of healed lesions and the mortality, follow in this series the same trend of distribution by age as in well tuberculized countries." Concerning the forms of the disease, he states:

There was nothing in the pathological alterations to make of these cases a group by themselves. Pulmonary changes were of the ordinary chronic type with caseation and cavitation. The upper air passages were found affected only in fatal cases, and so were the gastro-intestinal organs. It is to be noted that the pericardum, bones and lymph glands, other than the thoracic, were only exceptionally involved. In only 5 of the 76 non-lethal and healed cases, were lesions noted in the mesenteric lymph glands.

He concludes that "the anatomical character of the lesions in Puerto Rican whites and mulattoes is no different from that obtaining in well tuberculized peoples." The percentage incidence of lethal, subsidiary, healed and doubtful tuberculous lesions in 65 Negroes was nearly the same as in 365 whites and 175 mulattoes. However, out of six fatal cases in Negroes "two succumbed with predominantly glandular involvement; two with fairly extensive tuberculous pneumonias and two with generalized miliary tuberculosis." This, he points out, is suggestive of less resistance among the Negroes than among the whites and mulattoes; but the small number of cases in Negroes does not permit of definite conclusions.

Cavitation in childhood-type tuberculosis is rare, according to *Diagnostic Standards.* Only "occasionally" does such a lesion progress to excavation. However, in the series of 1,000 Puerto Rican cases studied by us, the X-ray pictures showed unmistakable excavation in 56 per cent. Moreover, the presence of fibrous tissue in large proportion was one of the notable features in 52 per cent of these plates. Many of the cases in which no cavitation was made out were of the purely fibroid type.

Puerto Ricans are often thought of in the United States as belonging to a separate, mysterious race, being neither white nor black. The fact is that three-fourths of the Puerto Ricans are white people of Spanish stock, while one-fourth are colored, mostly mulattoes. There are no Indians in Puerto Rico.

Although the tuberculosis mortality is 13 per cent higher among the colored than among the white people of Puerto Rico, we have noticed no marked differences in the forms of tuberculosis that occur in both races. This may be ascribed, first, to the fact that socioeconomic conditions do not differ greatly between white and colored, there being just as much indigence and overcrowding among the whites as among the colored; and, second, to the large admixture of white blood in the colored population. While about one-fourth of the island's inhabitants are colored, the total number of pure-blooded Negroes in the island, according

to the United States Census, did not exceed 50,000 in 1920, or less than 4 per cent of the total population.

The duration of the disease among hospital patients is less than among similar patients in the United States (22½ months among 500 adult patients who did not receive collapse therapy compared to 37 months among 2,537 patients at the State Sanatorium, Wallum Lake, Rhode Island (6)); but the patients of the government tuberculosis hospitals in Puerto Rico are far more indigent than the corresponding patients in the United States. The duration of the disease among patients of the middle class and the well-to-do is much longer, as evidenced in private practice. In one private clinic in San Juan the average duration of the disease among 80 patients not submitted to collapse therapy was 54 months. Of these 80 patients, 52 are still living, most of them being either quiescent or arrested.

Fibrous lesions of long duration seem to be more common among the higher classes than among slum-dwellers. This may or may not have to do with racial immunity, since the proportion of white people in the higher social strata is much larger than in the lower; but one gets the impression that the determining factors in the pattern and course of the lesion are, first, the intensity of the infection; second, living conditions, especially the amount of daily physical exertion; third, the promptness with which proper treatment is instituted. The healing forces of Nature have but a slim chance to do their work in the case of the stevedore, who, having been exposed to severe infection as a child from living successively with two or three cases of tuberculosis in the same room, sleeping on the same bed (or on the same floor), eating out of the same plate, begins to do strenuous physical labor from the age of 14, works twelve hours a day, feeds himself poorly, and, when he falls a prey to the disease, still must keep on doing his hard manual labor until no longer able to stand. It seems unnecessary to recur to the hypothesis of racial susceptibility to explain the severe, rapidly disseminating types of the disease that occur at times under such conditions. The wonder is that such cases occur in so small a proportion in our community, where the above conditions are the rule rather than the exception. This, if anything, is a proof of great racial immunity.

The definition of "childhood-type tuberculosis," as given in *Diagnostic Standards*, needs revision. That the lesions described as belonging to this type of tuberculosis do not always result from a first infection with the tubercle bacillus has been demonstrated again and again. One of

the most conclusive proofs was given in the report of the Tuberculosis Research Committee of the South African Institute for Medical Research (7), and was based on careful studies made on the native mine laborers of the Witwatersrand. Childhood-type tuberculosis was common among these Africans; yet 72 per cent of them reacted to a single intracutaneous dose with 0.1 cc. of 1:5,000 Old Tuberculin. "Stronger solutions," state the authors, "would probably show that 90 per cent are infected."

The childhood type of tuberculosis is said to be fairly common among the American Negroes; yet Aronson (8) found a higher incidence of tuberculin reactions among colored than among white in the South; and in Jamaica, where Opie (9) has reported a predominance of the childhood type of tuberculosis, the tuberculin test, according to the unpublished results of tests among many thousands of natives, shows that tuberculous infection is almost universal among adults living in urban areas.

Upon analyzing the characteristics of the childhood type of tuberculosis as expounded in *Diagnostic Standards*, one finds that they do not agree in all particulars with the reports of pathologists.

The characteristic that "the parenchymal lesion is usually localized in the lower lobe or lower part of an upper lobe" is denied by the study by F. R. Everett (10) who found, in an analysis of 402 autopsies, that "in more than half the negro adults with the childhood type of pulmonary tuberculosis the lesion has its origin in the apex of the lung." This same author reported cavitation in 18 out of 22 autopsies in adult Negroes with the childhood type of tuberculosis.

Pinner and Kasper (11) found that "tuberculous lesions in the Negro perforate more often than in whites." This finding is in conflict with the description of childhood-type tuberculosis as a lesion that only occasionally excavates.

Opie's statement (12) that "a larger number of colored than white persons escape tuberculous infection during childhood and in adult life suffer with an unusually severe type of the disease" can no longer be held as valid. Whatever the reasons for the severe tuberculosis occurring among the Negroes, we know definitely that the lack of tuberculization is not the cause.

We also know that pulmonary tuberculosis of the childhood type is not the severe disease that it was thought to be. W. M. Johnson and J. A. Myers (13) make this very clear in the following statement:

We have been too prone to talk about the great destructiveness of the first infection type of tuberculosis on insufficient evidence. Practically all recent

scientific observations have shown that it is rarely, if ever, very destructive whether it occurs in infancy or adult life. But reinfection, whether from exogenous or endogenous sources, or whether it occurs within a few weeks or many years from the time allergy develops, often results in destructive forms of tuberculosis, such as tuberculous meningitis, miliary tuberculosis or chronic pulmonary tuberculosis.

To the student of tuberculosis, the disparities of opinion, the contradictions and obscurities contained in the literature concerning the subject of childhood type tuberculosis are most confusing. One even wonders whether the distinction between a first-infection and a reinfection type of tuberculosis is justified; whether the pathological differences between the tuberculosis of children and that of adults could not better be explained on other grounds. When a child lives in close contact with a case of tuberculosis, it is being reinfected daily. After a few months of such close contact, whatever manifestations of tuberculosis it may exhibit will be the result of repeated infections. To separate the "first infection" from the "reinfections" under such circumstances is almost impossible; and these are the circumstances under which most tuberculous infections of any significance occur.

The present concept of childhood tuberculosis as a type of tuberculosis due to a first infection with the tubercle bacillus, we repeat, must be revised. The enormous amount of confusion that the improper use of this term, "childhood-type tuberculosis," has brought about, can only be amended by working out a standard definition based on recent epidemiological, clinical and pathological evidence rather than on mere impressions and opinions, however respectable their source.

SUMMARY

Tuberculosis mortality in Puerto Rico is five times higher than in the United States. The results of the epidemiological, clinical and pathological studies thus far carried out on the island point to extensive tuberculization and considerable immunity against the disease among the Puerto Ricans. Contrary to what has been stated in *Diagnostic Standards*, the childhood type of tuberculosis appears to be uncommon in Puerto Rican adults.

There are no marked differences between the forms of tuberculosis seen in white and mulattoes in Puerto Rico. Pure-blooded Negroes seem to show a greater tendency to lymphogenous and haematogenous spread: but this needs confirmation.

The frequent occurrence of "first infection" types of tuberculosis in subjects that are known to have been infected should afford enough ground for a complete revision of the present concepts of childhood and adult tuberculosis. The pathological differences between these two types of the disease should be explained on a more satisfactory basis than is afforded by the first-infection and re-infection theory.

Acknowledgments

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TUBERCULOSIS AMONG NEGROES IN THE UNITED STATES[1]

P. P. McCAIN[2]

In 1920, during the discussion of one of the earlier papers on tuberculosis among Negroes presented before the National Tuberculosis Association, one physician stated that whenever he heard of a Negro recovering from tuberculosis he considered that there had been a mistake in the diagnosis. While such a view was very extreme, it reflected in a measure the pessimism with which the whole subject of tuberculosis in the Negro was for many years regarded.

The steady decline in the tuberculosis mortality rate among Negroes as well as among whites, however, has given new hope and encouragement. As reported by Nelson (1), from 1920 through 1932 in the thirteen Southern States, the tuberculosis mortality rate in Negroes dropped 38 per cent as compared with 49 per cent for whites. It is all the more remarkable that this decrease in the Negro rate so nearly approached that in the white race, when we consider the poor economic status, the unfavorable environmental conditions, and the almost complete lack of facilities for fighting tuberculosis in the Negroes of the Southern States. Moreover, in the few places where facilities have been provided for the care of tuberculous Negroes it has been found that patients of this race, except those in the very far-advanced stages, usually respond favorably to treatment. They almost always coöperate fully, and they appreciate greatly the efforts in their behalf.

That tuberculosis in the Negro, however, still constitutes our most serious problem in the control of tuberculosis in the United States is emphasized by the following facts: In the Registration Area of the United States the tuberculosis mortality rate among our 11,000,000 Negroes is approximately three and a half times that of the whites, in most of our large cities it is four to five times, and among the ado-

[1] Presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936.

[2] North Carolina Sanatorium for the Treatment of Tuberculosis, Sanatorium, North Carolina.

lescent and young-adult groups it is from five to eight times that of the whites. Tuberculosis causes one out of every eight deaths among Negroes, but only one out of every twenty-one among whites. Although tuberculosis has dropped to seventh place as the cause of death among whites, it still stands second among Negroes. The complication of syphilis, which makes the prognosis less favorable, is very much more common in Negroes. Although Negroes constitute only 26 per cent of the total population of the thirteen Southern States, 53 per cent of the deaths from tuberculosis in these States occur in Negroes. Of the Negroes in the United States, 74.1 per cent live in the thirteen Southern States, where the per capita wealth is the lowest of any section of the country, and where there have been very few facilities provided for diagnosis, prevention and treatment of the disease among Negroes. In the North and West, where practically all Negroes live in large industrial centres, overcrowding and other poor environmental conditions obtain, and facilities for their care and treatment are very inadequate. The great majority of Negroes are from the very low income group, and the care of the tuberculous in this race will need to be financed almost entirely from public and philanthropic funds. Since such a large proportion of Negroes have positions as nursemaids for children, cooks, waiters, and butlers in the homes of the whites and in public eating places, the tuberculosis problem in the Negro is a very vital one for both races.

Five years ago the National Tuberculosis Association realized that the problem was of such importance that it appointed a Committee, with a full time physician as secretary, to make a special study of tuberculosis in the Negro. This Committee has been very active, it has assembled much useful information on the subject, and has aroused a great deal of interest. Its report, which will be published soon, should be a very valuable aid in directing efforts toward the control of tuberculosis in the Negro.

THE CAUSE OF THE HIGH MORTALITY RATE

As to the most responsible cause of the high death-rate in Negroes there has been much speculation. Some would explain it largely on the basis of a lack of racial resistance to tuberculosis, while others claim that it is due almost entirely to environmental conditions. The scope of this paper will not permit a detailed discussion of this phase of the subject, but undoubtedly both factors play a definite part in the high Negro death-rate.

LACK OF RACIAL RESISTANCE

In a report on a series of 303 very carefully performed autopsies on Negroes compared with 219 on whites Pinner and Kasper (2) have shown that, from a *pathological* standpoint, the disease in the Negro manifests characteristics which are indicative of lowered resistance. They found in the Negro a greater tendency to miliary tuberculosis in all ages; a more frequent involvement and caseation of lymph nodes, and this even in adults with calcified primary lesions; a greater tendency to lymphogenous and haematogenous dissemination; a greater tendency to massive exudative lesions with large circumfocal, often haemorrhagic infiltrations. They also noted generalized nodular metastatic lesions, which are rarely seen in whites. They state that "Infection tends to produce a high state of allergy in the Negro, but that he, unlike the white, does not readily acquire a state of increased resistance coincidently." Other workers have called attention to many of these same pathological characteristics in the tuberculosis of Negroes.

The *clinical* manifestations of tuberculosis in the Negro also point to a lower state of resistance to the disease than in the whites. The chronic apical type of tuberculosis, with alternating periods of spread and improvement so common in the white, is comparatively rare in the Negro. Subapical, central and basal lesions are much more common. Physical signs are relatively less pronounced and X-ray evidence relatively more so. Although two-thirds or more of the cases are in the far-advanced and less than 10 per cent in the minimal stage when first discovered, except those found in surveys of apparently healthy groups, practically all give a history of very short duration of symptoms. As would be expected from the usual type of their lesions, their symptoms are more acute, high fever, rapid pulse, night-sweats, pleurisy and pleural effusions being more common than in whites. Since the Negro is of a more phlegmatic temperament and less likely to notice mild symptoms, and less likely also to consult a physician for minor ailments, the onset may not be so acute in many cases as the history would indicate. Lymphatic and other extrapulmonary lesions are also considerably more common in this race.

The fact that, as a race, the Negro has less resistance to tuberculosis than his white neighbor, however, does not indicate that a large proportion of Negroes do not have a considerable degree of resistance. Many Negroes who are exposed to massive infection escape clinical disease. Surveys usually show that a larger percentage of Negroes give positive

tuberculin reactions than whites. During the last nine years the Extension Department of the North Carolina Sanatorium has given the tuberculin test to 172,000 white and to 32,000 Negro school-children of all ages, using 0.1 mgm. of Old Tuberculin intracutaneously, a very large porportion of both races being from strictly rural districts. Fourteen per cent of the whites and 18 per cent of the Negroes reacted positively. Approximately twice as large a percentage of the positive reactors among Negroes showed demonstrable lesions by X-ray as among the whites. They also showed more numerous and more extensive childhood lesions, more caseous lymphatic lesions and more frequent adult-type lesions. But the large number which showed numerous or tremendous calcified, presumably healed lesions without having had any treatment and often after having lived under the most adverse circumstances indicates a degree of resistance that inspires hope for eventual control in the Negro as well as in the whites.

THE INFLUENCE OF ENVIRONMENT

There are some who try to explain the high tuberculosis mortality rate in Negroes almost entirely on the basis of their economic status, their racial habits and their environment. There is no doubt of the fact that these factors play a part and probably a very large part in the high death-rate. Poverty and ignorance of the laws of hygiene are quite common among them. Overcrowding and poor ventilation are the rule. The indiscriminate commingling of friends and relatives with the sick is quite common. A large proportion of them are insufficiently clothed and poorly fed. Practically all the sick have to remain at home. Few can be isolated and few practice the necessary precautions to protect the others around them. Such conditions are ideal for producing lowered resistance and massive infection. It is really surprising that the mortality rate is not higher.

In a splendid survey of more than 8,000 Negroes of all classes in their city, the Pittsburgh Tuberculosis League, as reported by Witchen (3), found that the childhood type of tuberculosis was five times as prevalent among the Negro children of low economic status as among those in comfortable circumstances. This survey indicated that in the total Negro population of the city 8 per cent had tuberculosis in some form and that 4.5 per cent had active pulmonary tuberculosis of the adult type. The study, moreover, showed that 58 per cent of the cases with active adult tuberculosis and 39 per cent of those with positive sputum shared their

beds with one or more persons, and that 69 per cent of the active cases and 49 per cent of the sputum-positive cases shared their rooms with one or more persons. The authors found also that the relative number of hospital days for white tuberculosis patients in Pittsburgh exceeded by more than three times that of the Negroes.

In a study of mortality in Cincinnati for the period 1929–1931 by the Public Health Federation (4), it is reported that the Better Housing League of Cincinnati estimated that one-half the Negro population in Cincinnati is housed under bad conditions, one-fourth under fair, and one-fourth under good conditions. In the population classed as badly housed the Negro tuberculosis death-rate averaged 500 per 100,000; for those housed under fair conditions the rate was 250; and where good housing prevailed the rate was 93.

Conditions among the Negroes in Pittsburgh are a fair sample of conditions which obtain in most of the other large cities in the North and West. In most of these large cities the Negro tuberculosis mortality rate is very much higher than the average for the country as a whole and also considerably higher than in the smaller and less congested Southern cities and rural districts. In rural areas of the South, where live the great majority of Negroes, although opportunities for infection are not so great, housing conditions are very poor, and ignorance, superstition and poverty are probably even more rife than in the cities. In this whole area also there are practically no dispensary and hospital facilities for the Negro. In the whole thirteen Southern States there were in 1934 only 1,666 sanatorium beds for tuberculous Negroes besides those in Federal, penal and insane hospitals. In the same area there were in 1932 approximately 12,500 Negro deaths from tuberculosis.

RESPONSE TO TREATMENT

The degree of improvement which Negroes make under favorable conditions is encouraging. Under modern sanatorium treatment practically all minimal cases become arrested; most moderately advanced and even many far-advanced cases also respond favorably. Nothing like so large a percentage of the total number of Negroes treated in sanatoria become quiescent or arrested as of the whites, but this is largely due to the fact that, as above stated, a very much larger percentage of Negroes have far advanced and very active lesions when first discovered.

A few years ago some workers felt that Negroes responded so poorly

to compression therapy that it was hardly worth while using it in members of this race. During the last six years at the North Carolina Sanatorium we have employed pneumothorax in 228 and phrenicectomy in 147 Negroes. Our experience leads us to feel that, for similar types and extent of lesions, Negroes respond almost as well as whites to compression therapy. In 1933, Chadwick, Markoe and Thomas (5) reported the results in 464 Negroes treated in Detroit sanatoria, of whom 67 per cent were far advanced and 23 per cent moderately advanced, and in whom compression therapy was used in 70 per cent. They state that of the discharged cases 28 per cent were arrested, and of the cases still under treatment 53 per cent were showing a favorable response.

AFTER-CARE AND END-RESULTS

Since most Negroes can earn a livelihood only as laborers or as personal-service workers, the average Negro who secures an arrest of his disease is confronted with a serious problem in finding work which will offer him a living and which will not cause him to have a return of his disease. Naturally their former employers prefer servants who are known to be healthy for such tasks. Often arrested cases are forced to take less remunerative jobs which are very unsuitable for patients who have had tuberculosis. Under such conditions, with their poor environment, it is not surprising that a larger percentage of Negroes than whites have a return of activity.

HOW CAN THE SITUATION BE IMPROVED?

One of the most urgent immediate needs which we can reasonably hope to meet is the isolation of sputum-positive cases. The conditions surrounding most Negro homes are such as to make it impossible for a positive-sputum patient to take sufficient precautions to keep from infecting other members of the household. More sanatorium beds for Negroes are urgently needed. In the more wealthy cities of the North and West the institutional bed-capacity should be increased without delay until there are at least as many beds occupied by Negroes as there are Negro deaths. In most regions of the South, on account of financial conditions, the possibility of establishing sanatoria with sufficient beds for Negroes is out of the question now and will be for some years to come unless Federal aid should be made available. It should be possible, however, for all sections of the South to provide a gradual increase in beds up to the number needed.

In sections where sanatoria cannot be provided, the most practical way of handling the problem is the establishment of tuberculosis units in connection with county homes. Positive sputum cases whose homes are crowded can be isolated in such units and can be made comfortable at very low cost. Medical care is furnished by the county physician, the county health officer or by a local physician. Several of the counties in North Carolina have such units for both white and Negro patients and probably many of the counties in other States have made similar provisions.

In communities where nursing service is available Burr Cottages can be used during mild weather. They are a rather poor makeshift, however, for they often do not provide sufficient isolation for positive-sputum cases; during bad weather they are uncomfortable; and frequently there is no one in the home capable of supplying a suitable diet and nursing care for the patient.

THE PUBLIC-HEALTH NURSE

At present, where sufficient sanatorium beds are not available the public-health nurse is probably the most important factor in controlling tuberculosis in the Negro. Even rural areas can provide nursing service. Negroes rarely see a physician. It is said that in one Southern state 25 per cent of all the Negroes who die do not have the services of a physician, and this situation is probably pretty much the same in the other states of the South. It is the public-health nurse who visits the sick in their homes, provides sanitary supplies, shows them how to practice the necessary precautions, teaches the housewives what foods to use and how they should be prepared. She also discovers most new cases and makes arrangements for contacts to be examined.

NEED OF TRAINED NEGRO WORKERS

There is great need for more trained Negro workers. As demonstrated more than twenty years ago by Landis (6) at Phipps Institute in Philadelphia, the coöperation of Negroes can be secured to a much greater extent by the employment of nurses and physicians of their own race, who have knowledge of their prejudices and a sympathetic understanding of their problems.

Negro workers have been used in tuberculosis-control programs to such a small extent that there are very few places where they can get special training in tuberculosis. So far as the writer can find out,

there are only three tuberculosis training schools for Negro nurses in the United States. Few, if any, of the sanatoria give postgraduate courses for Negro nurses. Practical experience in sanatoria would add very much to the efficiency of public-health nurses. The increased number of both white and colored public-health nurses which will be made available through the Social Security Bill will be a great help, especially in the Negro, in efforts to control tuberculosis.

There is also great need for the training of Negro physicians in the diagnosis and treatment of tuberculosis. It is said that 90 per cent of Negro physicians graduate from the medical department of Howard University and from Meharry Medical School. Since tuberculosis constitutes such a serious problem for the race, it would be a most worthwhile expenditure if some of the philanthropists would provide special facilities at these two institutions for teaching tuberculosis in its various phases to their students.

The training of Negro internes in sanatoria is proving to be helpful, but there are so few sanatoria for Negroes that the number of internes who can be trained is very limited. In the Negro division of our institution we find that a Negro interne fits in very satisfactorily, and other institutions have had the same experience. After one, or better two, years in a sanatorium, these Negro physicians can go out and be leaders in the fight against tuberculosis in their race. The Atlanta Tuberculosis Association is using with great success a Negro physician, who was an interne at the Georgia State Sanatorium and who is now in private practice, to direct their Negro tuberculosis diagnostic and pneumothorax clinics. He is assisted by several other volunteer Negro physicians, all of whom are giving their services without charge. Essentially the same plan is being used in New Orleans and probably in other cities also. In Detroit, Negroes are being treated very satisfactorily in separate hospitals by Negro physicians who have had sanatorium training and who work under the supervision of the City Comptroller of Tuberculosis. Clinics or institutes at sanatoria and symposiums on tuberculosis at Negro state medical societies are also worthwhile methods of arousing interest and of furnishing information to Negro physicians.

NECESSITY FOR IMPROVED DIAGNOSTIC FACILITIES

Since tuberculosis is now being discovered in the minimal or curable stage in less than 10 per cent of its Negro victims, it is most evident that improved diagnostic facilities for the race are essential for better

control. Negroes are slow to consult physicians for most ailments. If, as usually happens in tuberculosis, they wait until they feel sick enough to consult a physician, the disease will be in the advanced stage before it is discovered. The majority will be too far advanced to be materially benefited and they will already have infected the other members of their households, thus making an endless chain of infection, disease and death. It is not enough to depend on old methods of diagnosis. Usually by the time definite physical signs can be elicited and by the time the sputum is positive the disease is in the well developed stage.

More general use of the tuberculin test and the X-ray are essential if cases are to be discovered early. It is especially important for all contacts to be tested and for the positive reactors to be X-rayed. Many who are apparently well will be found by this method to have early, but active, tuberculosis. Whenever a physician discovers a case of tuberculosis he should not only endeavor to trace the source of infection, but should have a study made of all close contacts. Employment of the tuberculin test and of the X-ray in all positive reactors will be most helpful in the study of large groups of apparently well persons, especially of adolescents and of young adults, such as public and high-school pupils, college students and industrial workers. There should be a regulation requiring all nursemaids, food handlers and other personal service workers, regardless of color, to be tested and for positive reactors to be X-rayed.

Since most Negroes fall in the charity or semi-charity class, private physicians cannot be expected to do any large proportion of this type of work. It will need to be financed through official and voluntary health and anti-tuberculosis agencies. Many Negroes, however, who cannot pay the regular charges will gladly pay for the cost of the X-ray films. From 40 to 50 per cent of the parents of the Negro children X-rayed in our school tuberculosis clinics pay one dollar for their children's films.

THE FLUOROSCOPE

The main objection to the extensive use of X-ray films is their cost. With the recently improved fluoroscopic screen it is now possible to detect practically all advanced and most minimal tuberculous lesions which are of clinical significance with the fluoroscope. The presence of lesions and also their extent can be determined very much more accurately by a careful fluoroscopic examination than by any other procedure

except by the making of X-ray films. The fluoroscopic examination can be made quickly and with practically no expense after a fluoroscope is provided. Satisfactory fluoroscopes can be had for $600 or $700, or perhaps a little less, and should be in much more general use. They can be used to great advantage in tuberculosis clinics, and even by small city and county health departments in the examination of contacts, suspects and servants. Capable health-officers or county physicians through intensive short courses in sanatoria can learn to use the fluoroscope well enough to diagnose the great majority of clinical cases of tuberculosis. In doubtful cases X-ray films should of course be made.

For use in our state-wide clinics the Extension Department of the North Carolina Sanatorium has recently got the Kelly-Koett X-ray Company to make portable fluoroscopes for us which can be carried in an ordinary coupe, quickly assembled and used by plugging in an ordinary light socket wherever alternating current is available. Through the use of a special hood, a dark room is not necessary. These fluoroscopes make it possible to examine many more patients per hour, and they increase materially the popularity of the clinics.

PNEUMOTHORAX CLINICS

In thickly settled Negro communities, pneumothorax clinics are helpful for administering refills of air to sanatorium ex-patients and also in compressing patients with unilateral disease in whom a satisfactory collapse can be obtained. They should be conducted only by competent physicians who are experienced in the diagnosis of tuberculosis and in pneumothorax technique. It is also essential that a fluoroscope be available. If at all possible, all patients should be in a hospital for at least a few weeks after the treatment is initiated. It would probably be better for patients with bilateral disease and for those with unilateral disease in whom only a partially successful collapse is obtained to be at complete rest in bed at home rather than to take the necessary exertion to go for refills of air. In North Carolina, which is largely a rural state with no large cities, there are approximately 100 physicians distributed all over the State who are experienced in giving refills of air. At present both white and Negro patients from any part of the State can get refills without traveling any great distance. Few of these physicians initiate pneumothorax treatment, however, and none of them do so unless the patient is in a hospital or sanatorium.

BETTER ECONOMIC AND EDUCATIONAL FACILITIES

Before we can hope for any control measures to be permanently effective in the Negro, it is necessary to improve his economic status and to educate him to a better understanding and appreciation of the laws of health and hygiene. We must provide for him better wages, better homes and better schools. Through health educational courses in Negro colleges and summer schools and through both practical and theoretical health teaching in public schools there is a great opportunity for teaching the pupils how to be healthy and of reaching the parents through their children. Negro teachers appreciate any health activities that are conducted in their schools. Negro pupils also manifest great interest in health activities. It has been found that essay contests in Negro schools and colleges are very effective in arousing interest and in getting Negro pupils to acquire information concerning tuberculosis. A better understanding of the laws of health on the part of the race will lead to a better economic status and to a permanent reduction in the morbidity and mortality both from tuberculosis and from other diseases.

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TUBERCULOSIS AND THE BUSH NEGROES OF DUTCH GUIANA

A Tuberculin Survey of the Inhabitants of the Tapanahoni River Region[1]

MORTON C. KAHN[2]

The question of tuberculosis among the American Negro is one which all workers in the field of this disease acknowledge to be of great importance from both the practical and academic points of view, and especially so in view of the number of problems involved when one considers the epidemiology and pathology of this disease as it occurs in Negro people.

Such problems as racial susceptibility *versus* economic status as an explanation of the prevalence of this disease in the black man in certain communities, come to the fore as subjects worthy of being illuminated.

As will be remembered, Jones and later Bushnell, stated that prior to the Civil War, the tuberculosis rate among Negro slaves in Charleston, South Carolina, was little if any higher than that of the white man. According to these observers, it was only after the slaves obtained their freedom, thus being forced as freed men to live and work under conditions less hygienic than those under which they had existed as slaves, that the higher tuberculosis rate among the blacks began to manifest itself. Bushnell stated that the proximity of the two races excludes the possibility of their not being equally exposed to the disease during the period of slavery. The frightful mortality following emancipation, he said, cannot be the result of primary infection, whereas the economic conditions under which the Negro has since labored cause poverty and unsanitary homes favorable to the development of tuberculosis.

Numerous other contributions have been made to this subject including those of Opie and McPhedran, Augustine, Bogen, Walsh and Mason, Drolet, Pinner and Kaspar, to mention but a few.

In order to possibly throw some light on the problem of the epidemi-

[1] Presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936. The present paper is an abstract of a more detailed and extensive study to be published by Doctor Kahn.

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ology of tuberculosis in the Negro, a tuberculin survey has recently been made on the Bush Negroes of the Tapanahoni region in Dutch Guiana. These people were selected because of their unique history. Transported to the northern part of South America as slaves, the Bush Negroes defeated the Dutch in a long series of bloody conflicts, and finally in 1760 a treaty of peace was signed. To-day, this group of Bush Negroes live in the wildest and most inaccessible part of Dutch Guiana, but have reverted to the same customs and type of existence as did their forebears in the forests of West Africa many years ago.

The Dutch Guiana Bush Negro is of identical blood with the North American Negro. The slave-ships supplying both places received their cargoes from the same parts of the West Africa Guinea coast. Some of the rebel slaves who escaped were the so-called salt-water Negroes, that is to say, those who had actually been transported from Africa. Most of them, however, had been born on the sugar plantations and in the towns of the colony. While it may be said that the majority of the escaped Negroes were field hands, it is known that a goodly proportion were also domestic help, cooks, house-boys, laundresses, concubines and artisans of various types, who had come into intimate contact with the not insignificant white population, and it is reasonable to assume that they suffered from tuberculosis to the same degree as white population in Europe.

The survey which we made was organized for tuberculin-testing alone, and the tuberculin used was the purified protein derivative (P.P.D.) developed by Seibert and Long and recommended as a standard by the Committee on Medical Research of the National Tuberculosis Association. A number of duplicate tests were also made with standardized Old Tuberculin as a check. The dosage and method of injection as recommended by the Committee were scrupulously followed, and at the beginning of the survey a second dose was given to those failing to react to the first. After the first 200 tests proved to be negative to both injections, it was deemed expedient to dispense with the first injection altogether (0.000,02 mgm.) and employ only the second (0.005 mgm.);—this, in view of the fact that the people are timid and very superstitious, and at times some difficulty was encountered in getting them to submit to the test.

In view of the difficulty of transportation which is feasible only in native dugout canoes, because the river contains innumerable rapids and falls, it was felt that the use of a portable X-ray apparatus would be

impractical, at least until a preliminary survey was made to determine the number of those reacting positively.

The expedition proceeded by sea from Paramaribo, the port of Dutch Guiana, to Albina 40 miles above the mouth of the Marowyne River, a stream that separates French from Dutch Guiana. At this point the equipment was loaded into dugout canoes and the Marowyne river was traversed to its source. The expedition then entered the Tapanahoni river which is the country inhabited by the upper Aucaner tribe of Bush Negroes.

The survey began at the village of Dree Tabiki (The Three Islands), which is the village of the Granman, or King, and extended up the river to the village of Gran Boree, the most remote of all Bush Negro villages in Dutch Guiana. Other villages visited for the purpose of making these tests were Sangamasusa, Peekehtee, Polo Kaba, Pekein, Condree, Mansie, Keesai, Lohabie, Gado Hollo and Affifasitti. Altogether 765 completed tests were made, not including 70 on Indians of the Alukuyana tribe. All of the Indians reacted negatively. As regards the Bush Negroes, 18 gave rise to positive reactions, or 2.35 per cent of the entire number tested. All of the reactors, however, were members of a single family group in one village and their huts were clustered together in the same part of this village. This situation at once gave rise to an epidemiological clue concerning the possible source of infection, so it was deemed advisable to attempt to locate the foci. This may or may not have been accomplished, but the situation pertaining to the attempt is as follows: Of the 18 reactors, 10 were women and two were female children. None of these had ever left the Bush Negro country. As concerns the remaining 6, four were men and two were boys and only two of the men had visited the trading post near the foot of the Marowyne river during the past five years. One of these only remained for a few days, returning almost immediately to his village. The other lived at the trading post for two years, during which time he also acted as guide to occasional groups of town Negroes who were seeking for gold in the newly opened French Guiana gold fields. He had returned to his village a scant five months before I saw him. Questioned closely as to pulmonary symptoms none of those showing the positive tuberculin tests complained of cough or pain in the chest, save the man who had been away from his village for a long time. He complained of a severe cough, and also stated that he was spitting blood. He complied with a request to bring a specimen of his sputum, and this was found to con-

tain a considerable amount of blood; also an acid-fast stain revealed large numbers of tubercle bacilli. It is evident that this man may be responsible for the spread of the infection in his village.

I immediately called a "Krutu" or Council, during which an attempt was made to explain the mode of transmission of tuberculosis. The Bush Negroes were cautioned against mixing with the gold-seekers and were also told to visit the trading post only when necessary and then to construct their thatch shelters away from the members of the post, and also to mix with them as little as possible. Detailed instruction in sanitation was also given to the man who appeared to have open pulmonary tuberculosis. However, the Bush Negroes have their own ideas on sanitation for, commenting on my use of the handkerchief, they constructed the following proverb: *"San Bahkra puttu Na en Sakka, Djuka T'chobo"*—What the white man puts in his pocket, the Bush Negro throws away.

Aside from the village mentioned, it is interesting to note that the upper Aucaner tribe of Bush Negroes seem to be entirely free from infection with the tubercle bacillus as evidenced by the tuberculin tests. Such a condition gives rise to a number of interesting speculations. In the first place, the Bush Negro must not be confused with certain aboriginal people who have never had contact with a tuberculized race. A number of the slaves who escaped lived in intimate contact with the white man for many years and some of these Negroes must have become infected prior to their fleeing into the jungle, but to-day (if a tuberculin survey is to be given full weight) there seems to be no remnant of this disease among them. In this condition they stand in marked contrast to their North American brothers, as well as to those Negroes living in the West Indies and the towns of Dutch Guiana. What is responsible for this difference? Unquestionably the isolation of the Bush Negro plays a part, although this is not entirely complete. Many of them visit the trading post periodically, and also the so-called Devil's Island Penal Colony, which is just across the river from this post. However, a considerable number of the tribesmen are content to remain in their own territory.

The villages of the Bush Negroes are universally clean and sanitary. There is no filth or debris gathered about. Their huts made of thatch are large and spacious preventing overcrowding, and usually open at both ends which ensures excellent ventilation. They take frequent baths in the river on the banks of which their villages are always located,

and as far as the so-called characteristic Negro odor is concerned I found it to be entirely lacking. The diet appears to be adequate in calories, but deficient in protein, consisting for the most part of cassave and upland rice, supplemented with what fish and meat they are able to procure, sometimes not very much of the latter to be sure.

The clothing consists of a loin-cloth and camissa for the men and a width of cloth about the lower limbs for the women. This is sufficient for the climate and ensures an abundance of sunlight for their skins. Their entire economy seems to be healthy from most points of view, but malaria and yaws takes a rather heavy toll among the children.

From the point of view of tuberculous disease, however, the relation of the Bush Negro to enforced labor seems worthy of consideration. The Bush Negro has no boss, unless such a person be his wife. When he is tired hunting, fishing or polling his heavy dugout canoe, he simply rests, and no amount of urging is sufficient to make him continue unless he wishes to do so. This is in contrast to the Negro working in other regions where the hours are often long and the food and housing at the close of the day far from adequate.

Are the Negroes primarily a tropical forest-dwelling people, as immune to the rigors of enforced labor as we sometimes believe to be the case? It is my impression that the social and economic sides of the situation should be given full consideration when studying the problem of the susceptibility of the black man to tuberculosis.

BRIEF COMMENT ON RACE AND TUBERCULOSIS[1]

MAX PINNER[2]

In trying to open the discussion of the papers of this symposium, I am confronted with the impossibility of doing justice to the wealth of interesting data and opinions that have been presented. In the brief time at my disposal I can attempt only to point out what seem to me to be some of the high lights of the papers to which you have just listened. The question of paramount interest to us all in this matter is whether or not true racial genotypic differences exist in the susceptibility to and in the development of tuberculous disease. Some of us in the United States feel that such differences exist; this was indicated by Dr. Long's remarks in regard to American Indians and by Dr. McCain in his observations on American Negroes. In our pathological studies which we published a few years ago, we arrived at the same conclusion. On the other hand, Dr. Alarcón and Dr. Rodriguez Pastor were definite in their statements that such genotypic differences are not demonstrable in their populations. This apparent discrepancy of opinions is probably not as inexplicable as it appears on the surface. The last-named speakers made their observations in what we may call the natural habitat of their respective groups of people, while we in the United States see representatives of the same races under the stress and strain of maladjustment and under unfamiliar and frequently unfavorable living conditions. It is quite possible that adverse living conditions bring into clear manifestation some genotypic differences that remain hidden when the same people live under conditions that are for them normal by virtue of habituation and therefore adequate.

It should be emphasized in Dr. Alarcón's paper that the tuberculosis mortality in Mexico City declined from 500 to 130 during the first 30 years of this century without the benefit of any organized effort to combat the disease. This is mentioned, not in order to belittle, or even to

[1] A summary *Discussion* of papers presented at a Joint Symposium of the Pathological, Clinical, Sociological and Administrative Sections of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 25, 1936. See AMERICAN REVIEW OF TUBERCULOSIS, 1937, *35*, pp. 1, 6, 13, 25 and 36.

[2] Oneonta Tuberculosis Hospital, Oneonta, New York.

question the value of an organized tuberculosis campaign (which exists now in a highly developed form in Mexico City), but to point out that statistical variations in tuberculosis are, at least in part, dependent upon factors that are apparently incompletely known and not subject to our conscious control. The Republic of Mexico may yet become a most interesting proving ground for the various theories in the epidemiology of tuberculosis; for here we find, side by side, excessive and practically zero tuberculosis mortality, wide variations in regard to climatic conditions between the tropical seashores and the high plateau, thoroughly tuberculinized populations, such as in the harbor town of Vera Cruz and communities practically untouched by the infection in some remote communities in the mountains, completely rural and highly industrialized districts, and a wide variety of races and racial mixtures.

Dr. Rodriguez Pastor should be highly complimented for his vigorous attack on the unfortunate term "childhood-type tuberculosis." His discussion has shown from an important angle how much confusion this term has created. I hope that we may have in Dr. Rodriguez Pastor a powerful ally in what I hope will be a final frontal attack on "childhood-type tuberculosis." At the same time, however, it will be necessary to retain some clearly defined, and preferably descriptive terms, to distinguish primary and secondary infections.

Dr. Kahn's survey among the Bush Negroes of Dutch Guiana transcends by far in interest and importance a mere travelogue. He has discovered what might be called the primordial beginning of a tuberculosis epidemic in a completely nontuberculized population. It should be of greatest interest to find out, after a few years, the eventual consequences of the endemic nucleus that Dr. Kahn has uncovered. We hope that he will be able to report to us upon later studies.

I believe that this whole symposium is of greatest interest, not in spite of, but because of the divergent facts and views that were so ably presented. The apparent discrepancies forcefully emphasize the fact, so often forgotten in specialized studies, that no one single factor can explain or has sovereign importance in the epidemiological and pathogenic behavior of tuberculosis. While it seems likely that race is one of these factors, it is certain that living conditions in the broadest sense of the word are of great importance and that many other factors, known and unknown ones, determine the course of events.

THE DISTRIBUTION OF TUBERCULOSIS MORTALITY IN SOUTHEASTERN UNITED STATES[1, 2]

C. C. DAUER[3] AND L. L. LUMSDEN[4]

Most recent discussions on mortality from tuberculosis have been concerned with the decline in the death-rates from this disease and possible reasons for the decline. This paper presents the results of a study of the mortality in a fairly large section of the United States with the county as a unit. It deals especially with the distribution of mortality in the Southeastern States, the possible influence of certain environmental, economic and social factors on tuberculosis mortality in this area, and also the mortality rates by race, sex and age, as compared with those in other parts of the country.

TUBERCULOSIS MORTALITY IN THE UNITED STATES

The statement is frequently made that mortality from tuberculosis in the United States has been highest in the Southwestern and in the Southeastern States. In the Southwest, mortality rates from tuberculosis have been excessively high because of the large number of nonresidents who have migrated to that region for the purpose of seeking

[1] Presented at a session of the Sociological Section of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

[2] In 1932, through the combined efforts of the Tuberculosis and Public Health Association of Louisiana and the Health Committee of Council of Social Agencies in New Orleans, a project for a survey of tuberculosis in Louisiana was developed. The Louisiana State Board of Health and the Board of Health of New Orleans approved the project and requested the coöperation of the United States Public Health Service in making the survey. Dr. L. L. Lumsden, Medical Director, was assigned by the Surgeon-General to carry on the survey. This study was carried out in 1933 and 1934 in coöperation with various official and nonofficial health agencies in Louisiana, and had the approval of the National Tuberculosis Association. The report of the survey was published in *Public Health Bulletin No. 219*, entitled "A Survey of Tuberculosis in Louisiana." Following the publication in 1935 of the survey in Louisiana the authors of the present paper collaborated in extending the study of tuberculosis mortality in other states. Certain details of that study are presented in another *Public Health Bulletin No. 225*, under the title of "Some Features of Tuberculosis Mortality Distribution in the United States." The present paper represents the result of further analysis of data accumulated in the study reported in *Public Health Bulletin No. 225*.

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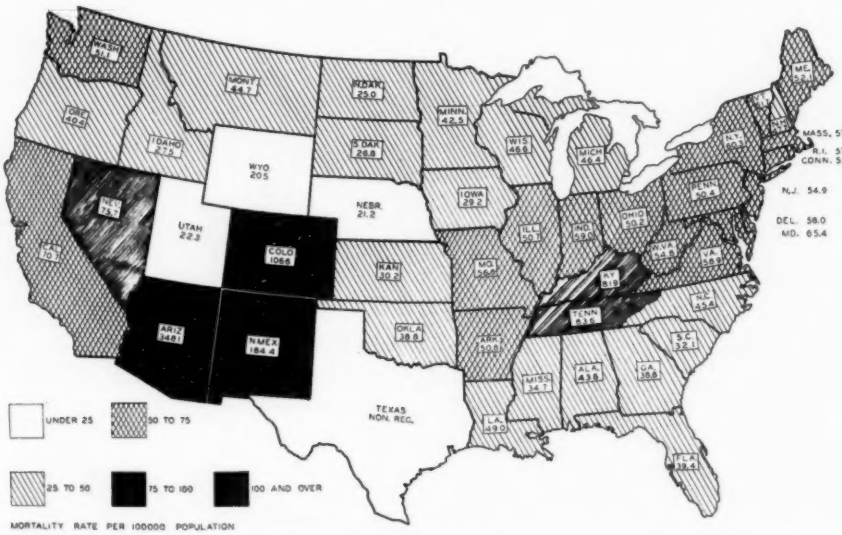
[4] United States Public Health Service.

a cure for tuberculosis. In the southeastern section of the country mortality for the total population has been high because of the large proportion of Negroes in the total population. The somewhat commonly expressed view that the rates for both whites and Negroes in this section are high is erroneous. When the rates are analyzed for white and colored populations separately, this fact becomes apparent.

For instance, map 1 shows the average annual mortality rates in 47 States for all forms of tuberculosis in the white population during the five-year period, 1929 to 1933 inclusive. Only two Southern States, Tennessee and Kentucky, had rates much above that for the Registra-

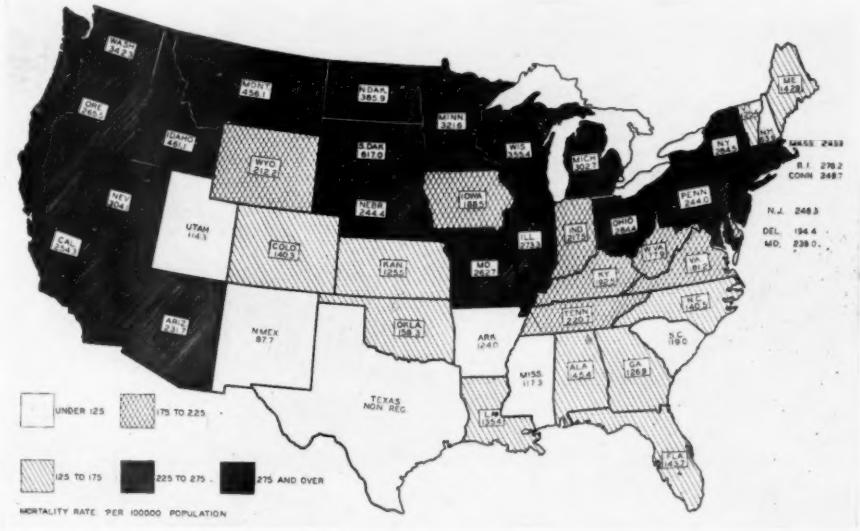


Map 1. Average annual mortality rate per 100,000 population from all forms of tuberculosis in the white population by States, 1929–1933

tion Area as a whole (56.5 per 100,000 population), and two others, Virginia and Maryland, had rates approximately equal to that for the Registration Area. In the East North Central, North Atlantic and several New England States, mortality rates for white persons were approximately the same as that for the Registration Area. The rates for the states south and southwest of Tennessee and Virginia were considerably lower. The Southwest had excessively high mortality rates, while the Northwest had relatively low rates for white persons.

For the colored population the mortality from tuberculosis has shown distinct geographical differences. All Southern States (see map 2)

have had lower rates than those in the States in the North. It should be noted that west of the Mississippi River, except in the West South Central group of states, the colored population consists principally of Indians or of Indians and Mexicans.[5] East of the Mississippi River the colored population is almost entirely Negro. In the eastern half of the country the colored population of the South differs materially from that of the North in that the former is largely rural while in the North it is more than 90 per cent urban. This fact has perhaps a bearing on the differences in mortality from tuberculosis among Negroes in the two areas. However, the records show that Negro death-rates from tuber-



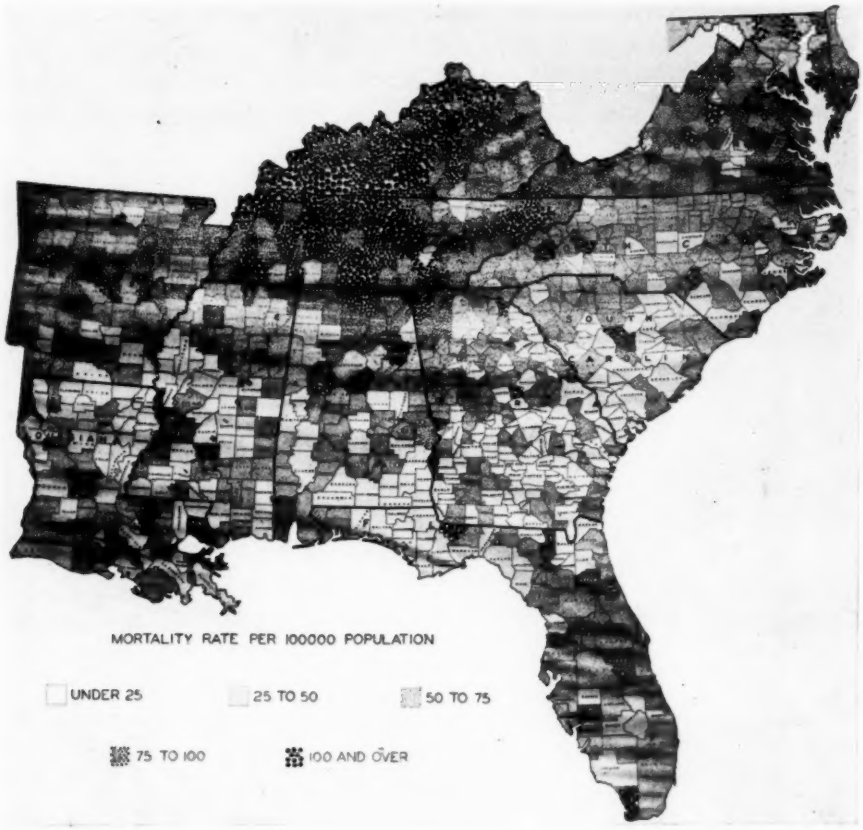
Map 2. Average annual mortality rate per 100.000 population from all forms of tuberculosis in the colored population by States, 1929–1933

culosis in cities of the South have been lower than those in the North; and there is doubt whether crowding in the northern cities has been much greater than in the southern cities to account for the wide differences in tuberculosis mortality. Climatic conditions which induce Negroes to remain indoors, a greater incidence of acute respiratory infections, employment in occupations hazardous to general health, and other conditions detrimental to the welfare of Negroes, have probably

[5] The comparatively low recorded tuberculosis death-rate for the colored in New Mexico is due largely to the fact that deaths among Indians in that State are not included in the mortality statistics of the State Department of Health.

been factors of considerable importance in causing the great difference in tuberculosis mortality in the two groups of cities. Perhaps the difference in age-distribution has also been a considerable factor.

From a very superficial study of maps 1 and 2 it is evident that many parts of the South have experienced comparatively low tuberculosis mor-

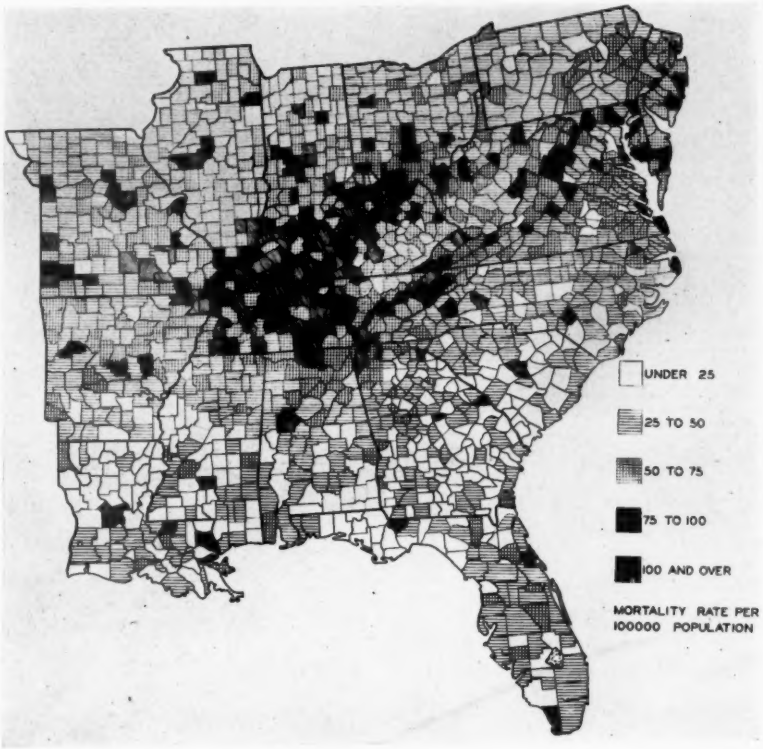


Map 3. Mortality from all forms of tuberculosis in the white population by counties in Southeastern States, 1929–1933

tality rates for both races. The colored as well as white mortality in the South, except in Kentucky and Tennessee, compares favorably with that of any other section of the country. (A more detailed discussion of these differences was made in the report published in *Public Health Bulletin No. 225.*)

TUBERCULOSIS MORTALITY BY COUNTIES IN SOUTHEASTERN UNITED STATES

It has been more or less common knowledge that Kentucky and Tennessee have had high tuberculosis mortality rates for both white and colored populations. The impression one is apt to gain from a study



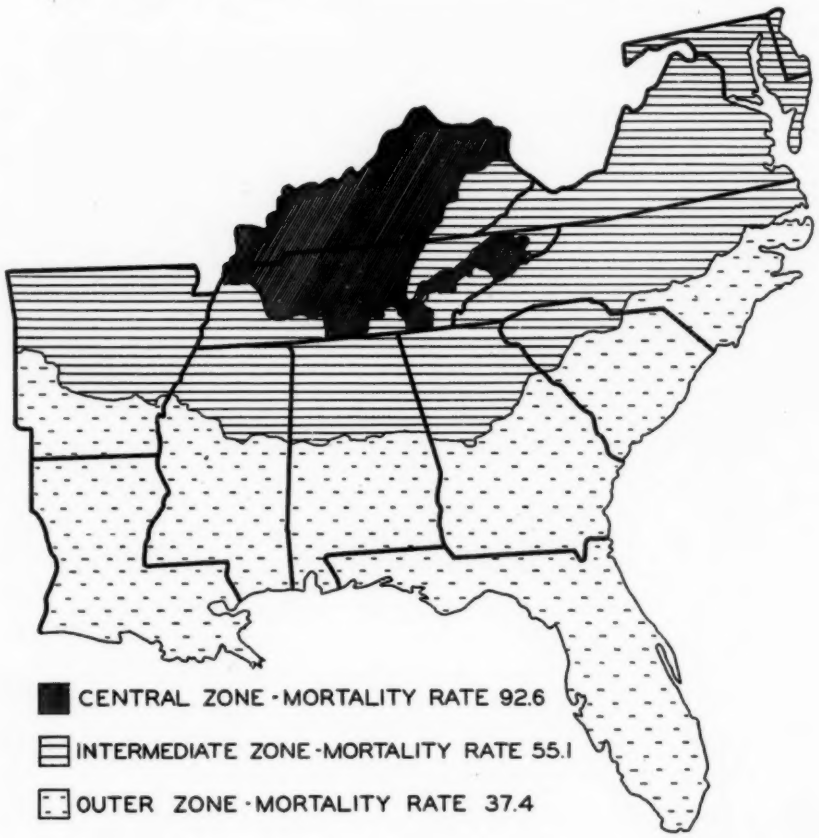
Map 4. Mortality from all forms of tuberculosis in white population of Southeastern United States, 1929–1933

of mortality in these two States, in contrast to those immediately bordering them on the north, south, and west, is that death-rates from tuberculosis decline abruptly as soon as one leaves either Kentucky or Tennessee. How erroneous such an impression is can be shown by a study of the mortality by counties.

Through the willing coöperation of State registrars of vital statistics and from reports of State departments of health the authors were able

to collect the number of deaths from all forms of tuberculosis for every county in twelve Southern States for the white and colored populations separately, covering the five-year period, 1929 to 1933 inclusive. Death-rates are plotted as five-year averages on maps 3, 4 and 5.

On the maps showing the mortality for white persons by counties

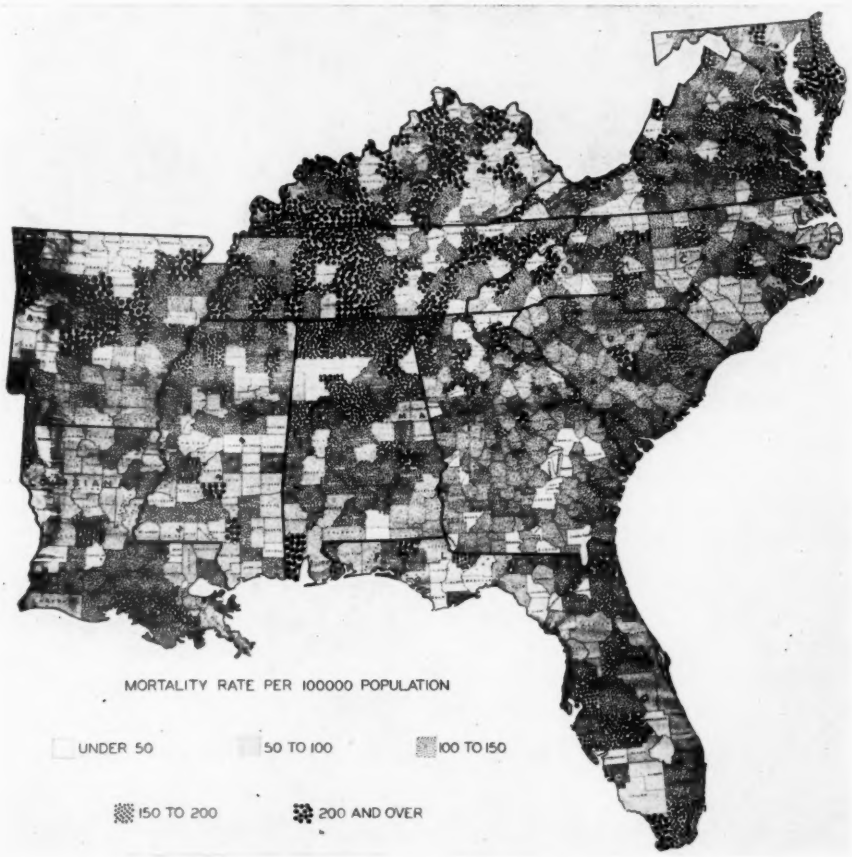


Map 5. Tuberculosis mortality by zones in the white population of Southeastern States, 1929–1933

there is a fairly well-defined area of high mortality centering in central Tennessee and in western and northeastern Kentucky. To a lesser extent this area of high mortality extends through eastern Tennessee and the western part of Virginia. In all directions from the central area in Tennessee and Kentucky tuberculosis mortality gradually becomes lower.

The whole area comprising the twelve Southeastern States was divided

roughly into three zones or regions according to mortality rates for white persons. The central zone, as shown in map 6, had the comparatively high tuberculosis mortality rate of 92.6 per 100,000 population. The intermediate zone, comprising western Tennessee, northern Arkansas, northeastern Mississippi, northern Alabama, northeastern Georgia,



Map 6. Mortality from all forms of tuberculosis in the colored population by counties in Southeastern States, 1929–1933

western South Carolina, western North Carolina and the major portions of Virginia and Maryland, had a rate of 55.1. The third zone, made up of southern Arkansas, all of Louisiana and Florida, the southern parts of Mississippi, Alabama and Georgia, and the eastern sections of South Carolina and North Carolina, had the comparatively low rate of 37.4

TABLE 1

Relation of tuberculosis mortality to social and economic factors in sections of Southeastern States

STATES AND LOCATION OF GROUPS OF COUNTIES	TUBERCULOSIS DEATH-RATE FOR WHITE POPULATION, 1929–1933	PERCENTAGE COMPOSITION OF POPULATION 1930[1]		PERCENTAGE DISTRIBUTION OF WHITE POPULATION 1930[1]			PER CENT OF ILLITERACY IN WHITE POPULATION OVER 10 YEARS OF AGE 1930[1]	ASSESSED VALUATION OF ALL PROPERTY PER CAPITA OF WHITE POPULATION 1932[2]	PERCENTAGE DISTRIBUTION OF WHITE PERSONS 10 YEARS AND OVER ENGAGED IN GAINFUL OCCUPATIONS, 1930[1]		
		White	Colored	Rural	Village	Urban			Agriculture	Industrial and Manufacturing	All Other Occupations
Alabama											
North	61.5	86.0	14.0	70.0	18.0	12.0	6.4	409	64.6	17.6	17.8
Central	43.1	53.5	46.5	33.5	25.5	41.0	3.5	993	28.3	31.5	40.2
South	29.7	64.5	35.5	53.7	24.5	21.8	5.4	627	51.1	20.2	28.7
Arkansas											
North	55.0	77.2	22.8	60.0	19.0	21.0	4.0	371	55.9	12.2	31.9
South	38.1	65.1	34.9	52.4	25.6	22.0	2.4	482	50.7	17.5	31.8
Florida											
Entire State	39.4	70.6	29.4	19.2	27.4	53.1	2.1	506	20.3	34.5	45.2
Georgia											
North	45.3	67.2	32.8	42.6	22.5	34.9	3.1	701	36.2	29.5	34.3
South	24.4	55.7	44.3	55.0	21.4	23.6	3.6	670	49.1	16.9	34.0
Kentucky											
Southeast	56.9	97.8	2.2	49.4	34.2	16.4	9.0	578	45.1	31.5	23.4
North and West	91.0	89.6	10.4	46.4	21.1	32.5	4.8	1488	41.2	23.2	35.6
Louisiana											
Entire State	49.0	63.1	36.1	34.2	22.2	53.6	10.7	872	29.4	22.8	47.8
Maryland											
Entire State	65.4	83.1	16.9	14.2	25.7	60.2	1.3	940	11.6	37.1	51.3
Mississippi											
Northeast	39.8	52.5	47.5	71.2	16.9	11.9	2.9	573	61.2	8.9	29.9
South	28.8	47.2	52.8	54.8	21.7	23.5	2.7	767	50.6	14.6	34.8
North Carolina											
East	36.4	55.9	44.1	55.0	24.1	19.9	5.7	1259	53.7	14.8	31.5
West	35.5	73.1	26.9	48.6	28.4	23.0	5.7	1235	37.6	35.0	27.4

[1] From 1930 Census reports.

[2] From "Financial Statistics of State and Local Governments: 1932," Department of Commerce, Washington, D. C. 1935.

TABLE 1—*Concluded*

STATES AND LOCATION OF GROUPS OF COUNTIES	TUBERCULOSIS DEATH-RATE FOR WHITE POPULATION, 1929–1933	PERCENTAGE COMPOSITION OF POPULATION 1930[1]		PERCENTAGE DISTRIBUTION OF WHITE POPULATION 1930[1]			PER CENT OF ILLITERACY IN WHITE POPULATION OVER 10 YEARS OF AGE 1930[1]	ASSESSED VALUATION OF ALL PROPERTY PER CAPITA OF WHITE POPULATION 1932[2]	PERCENTAGE DISTRIBUTION OF WHITE PERSONS 10 YEARS AND OVER ENGAGED IN GAINFUL OCCUPATIONS, 1930[1]		
		White	Colored	Rural	Village	Urban			Agriculture	Industrial and Manufacturing	All Other Occupations
South Carolina											
East	24.0	38.7	61.3	54.1	26.6	19.3	5.2	465	51.7	16.3	32.0
West	30.1	64.8	35.2	41.6	37.1	21.3	5.3	396	35.2	40.6	24.2
Tennessee											
East	80.1	91.6	8.4	43.7	24.0	32.3	6.6	629	36.0	31.8	32.2
Central	95.5	83.4	16.6	58.9	23.0	18.1	5.5	772	48.8	19.3	31.9
West	75.8	66.7	33.3	41.3	11.4	47.3	2.9	1056	40.8	17.3	41.9
Virginia											
East	57.1	59.6	40.4	33.3	32.2	34.5	2.7	1705	20.8	26.0	53.2
Central	50.7	70.9	29.1	52.6	25.0	22.4	5.8	981	38.2	27.2	34.2
West	64.4	97.8	2.2	45.4	37.4	17.2	10.2	430	44.0	28.1	27.9

The higher mortality rates for the colored populations for these twelve Southern States have shown a distribution quite similar as to those for white persons, that is, a central area of high mortality in Tennessee and Kentucky. It is not without significance that the mortality rates for both whites and colored were not the highest where the proportion of Negroes in the total population is greatest.

A more detailed discussion of the mortality rates for both white and colored populations by counties in these twelve States is presented in *Public Health Bulletin No. 225* referred to above.

A study of the distribution of tuberculosis mortality by counties in the southeastern section of the United States, in relation to certain factors sometimes suggested as being directly or indirectly related to the disease, reveals a number of interesting points. These can be brought out by limiting our discussion to the relationship of tuberculosis mortality among white persons to such factors.

Each of the eight States lying in the central part of the area shown on maps 3 and 4 was divided into two or more regions according to the general distribution of tuberculosis mortality. For instance, Alabama was divided into three regions or sections, the northern having higher

rates than either the central or southern sections. Since all of Louisiana and Florida lie within the zone of low mortality and Maryland within the intermediate zone, these States were not divided into sections. Mortality rates for these sections are shown in table 1, along with certain other data on social, environmental and economic conditions.

1: Physiographic and Climatic Conditions: As previously pointed out, the entire area under consideration can be divided into three zones or regions with respect to tuberculosis mortality. The outer zone of low mortality roughly comprises the low coastal plain of the South Atlantic seacoast and the Gulf of Mexico where the soil is sandy or alluvial. The intermediate zone is partly rolling tableland and partly mountainous. The central zone of high mortality is a plateau of rolling tableland. Most of this latter region has an underlying limestone formation, and a small part of it is sandstone.

There are no wide variations in meteorological conditions in the southeastern section of the United States except for a small section of the Gulf Coast and the Florida peninsula. The average annual temperature varies from 52°F. in the Cumberland Mountain plateau in eastern Kentucky and Tennessee to 75° in the southern part of Florida. Most of the States have average annual temperatures between 60° and 70°. The average yearly rainfall ranges from 40 to 45 inches in the central zone to 55 to 58 inches along the coastal region. There is little variation in relative humidity, the averages ranging between 65 and 71. There is also very little variation with respect to percentage of possible sunshine, the extremes being 54 and 66 per cent. However, there may be considerable variation in the actual quantity or concentration of actinic (or ultraviolet) rays reaching the level of the ground in the various sections of the southeastern states. There are no data available at the present time to give such quantitative measurements.

2: Prevalence of Other Diseases: Except possibly for certain acute respiratory infections there is no direct evidence to indicate that the presence or absence of other diseases or groups of diseases importantly influence the regional distribution of tuberculosis mortality in the South.

Mortality rates from certain respiratory diseases such as pneumonia and influenza have been higher in Tennessee and Kentucky than in the other Southeastern States. One should be very cautious about assuming that there is any causal relationship between a high mortality from

other respiratory diseases and that from tuberculosis, because a high degree of correlation alone is no proof. The same factor or factors may account independently for a high mortality from both causes, or different and unrelated factors may be responsible for high death-rates from each group of causes.

Typhoid fever, as judged by mortality rates, has been very prevalent along the entire alluvial valley of the Mississippi River, in Kentucky and Tennessee, and also the coastal plains of Georgia and South Carolina. Malaria has shown somewhat the same distribution except for its absence in central and eastern Tennessee and Kentucky. Hookworm disease has been most prevalent along the coastal plains where the soil is sandy. Certain other parasitic diseases, such as ascariasis, have been more prevalent in the mountainous regions of Tennessee, Kentucky, Virginia and North Carolina. Pellagra has been most prevalent in Mississippi, South Carolina and North Carolina.

3: Economic Status: The statement is frequently made that tuberculosis occurs more frequently and severely among the lower economic classes. However nearly true this statement may be, there is evidence that certain groups of counties with a comparatively low economic rating, as judged by the per capita assessed valuation of all property, have lower tuberculosis mortality rates than have other groups with very much higher ratings. It must be admitted that per capita assessed valuation is a crude index of economic status or economic resources, but it is the only one now available to us. The possibility exists that one area with a low per capita valuation may have a subsistence level sufficient to keep all except a very small proportion of the population well above the point of dire want, while another area with a higher valuation may have a subsistence level near or below the point of dire want for a larger proportion of the population.

From the data presented in this paper it appears that per capita assessed valuation based on the white instead of the total population has no direct bearing on a high or low tuberculosis mortality. For instance, South Carolina, with a low valuation, has a low tuberculosis mortality, while central Tennessee, with a higher valuation, has a higher tuberculosis mortality. It is probably true that tuberculosis does occur most frequently among those in the lower economic groups in any given community, but the evidence in this paper suggests that, when comparing one community with another, there are more important factors than

economic status which determine the relative rates of mortality from tuberculosis in the two areas.

4: Occupation: Tuberculosis mortality has been said to have a direct relationship to the extent of industrial development, that is, in highly industrialized centres tuberculosis, as judged by the mortality rate, is said to be relatively more frequent.

An attempt was made to determine the relationship, if any, between the tuberculosis mortality and percentage of persons engaged in manufacturing and industrial occupations of the various sections or States. The evidence found is very conflicting. In some States the section with the larger percentage of persons engaged in industrial occupations had the higher tuberculosis death-rates and in other States the opposite was the case. In South Carolina, where there was a great variation in the eastern and western sections of the state as to proportion of persons engaged in industrial pursuits (16.3 and 40.6 per cent, respectively) the tuberculosis death-rates did not show a great difference. (See table 1.) When the western section of South Carolina was compared with central Tennessee there did not appear to be a direct relationship between industrial development and tuberculosis mortality. The percentage of persons engaged in industrial and manufacturing occupations was 19.3 in central Tennessee and 40.6 in western South Carolina, while the tuberculosis mortality rates were 95.5 and 30.1, respectively. A similar lack of relationship was found for other sections of Southern States.

There was an insufficient amount of information available for separation of the industrial occupations into single industries, such as mining, iron- and steel-processing, quarrying and others, for each section of the Southern States. A more accurate estimate of the influence of any occupation on tuberculosis mortality in the South could be gained by tabulating the occupations of those dying of tuberculosis by a method similar to that used by Jessamine Whitney in compiling the data in her report on *Death Rates by Occupation*. Such information is not available at the present time.

The evidence presented in this paper also suggests that the percentage of population engaged in agriculture or in other nonindustrial occupations has likewise had no direct relationship to tuberculosis mortality. These data are presented in table 1.

5: Urban and Rural Populations: The population of the southeastern section of the United States has always been predominately rural rather

than urban. In recent years there has been some shifting from rural to urban because of the development of certain industries in the South. However, the 1930 Census showed that approximately one-half of the white population still lives in open-country (farm) communities.

For many years tuberculosis mortality apparently was higher in the cities than in the rural areas of the United States. There is evidence, however, that the urban has fallen faster than the rural rate, so that the difference has steadily diminished, and in the last few years the recorded urban rate has declined to below that for the rural. It must be remembered, however, that many sanatoria have been located in "rural" areas and that deaths in these institutions are not allocated to the usual residence of the decedents. This suggests that the diminishing difference may be more apparent than real.

TABLE 2

Mortality rates per 100,000 population from all forms of tuberculosis for white and colored populations of the entire State, urban, and rural areas for certain Southern States

STATE	YEARS	WHITE			COLORED		
		State	Urban[1]	Rural[2]	State	Urban[1]	Rural[2]
Alabama[3]	1930–1932	46.9	43.3	47.9	152.6	202.1	137.7
Florida[3]	1933–1934	36.2	45.6	31.3	136.8	195.7	102.2
Kentucky	1930–1933	74.8	65.9	80.3	204.0	203.5	204.2
Mississippi	1934	30.3	37.8	29.1	88.5	156.8	81.5
North Carolina[3]	1932–1933	36.7	55.5	32.6	131.4	212.3	109.6
Tennessee[3]	1933–1934	73.0	63.3	76.1	183.5	219.5	155.9

[1] Urban includes only cities of 10,000 population and over.

[2] Rural includes cities and towns 2,500 to 10,000 population.

[3] Rates corrected for residence.

It seems that the area of high tuberculosis mortality centering in Tennessee and Kentucky cannot be accounted for by a greater concentration of population in cities in that area.

It is a matter of interest that in recent years urban tuberculosis death-rates for the white population of the South have in many instances been slightly lower than in the rural districts. This has been so in Alabama, Kentucky and Tennessee—States in which certain sections have relatively high tuberculosis mortality rates. Three other States, where mortality has been considerably lower (Florida, Mississippi and North Carolina), have shown slightly higher rates in the urban than in the rural areas.

Negro tuberculosis mortality generally has been higher in urban than in rural areas, without respect to the regional location of the cities.

6: Racial Composition of Population: The Southeastern States were settled mainly by immigrants or the descendants of immigrants from England and Scotland. A few of the early settlers came originally from Germany and Ireland, but these constituted a small minority. Except in certain sections of Louisiana, with a considerable number of inhabitants of Spanish or French descent, most of the white population of the entire South came originally from Anglo-Saxon stock. At the present time there are few foreign-born. There appears to be no evidence that the national origin of the white population in Kentucky and Tennessee accounts for the high tuberculosis death-rates in that region, since most of the whole South was settled originally by Anglo-Saxons.

The Negroes of the South have been concentrated in the region of the "cotton belt," which lies along the Atlantic coastal plain and along the alluvial valley of the Mississippi River. The statement frequently has been made by some observers that the percentage of colored persons in the total population appears to have a direct relationship to the tuberculosis mortality rate for white persons. It is quite apparent from the data in table 1 that the sections of States with the highest percentage of Negro population are in most instances those which have had the lowest tuberculosis death-rates among white persons.

7: Education: Ignorance as well as poverty has been said by many to be directly related to the prevalence of tuberculosis. If the amount of illiteracy found in a State or section of a State may be taken as a rough index of the intelligence level of a community, it might be expected then that the highest tuberculosis death-rates in the white population would be found in sections with a high percentage of illiteracy. However, this is not true generally in the South. Some sections have had low tuberculosis death-rates along with a high percentage of illiteracy (see table 1).

TUBERCULOSIS MORTALITY BY AGE AND SEX

An interesting fact is that the distribution of tuberculosis mortality by age and sex has been generally quite different in the Southeastern States from that in the remainder of the Registration Area. Table 3 shows for these two groups of States the mortality rates per 100,000

population for all forms, pulmonary, and nonpulmonary forms of tuberculosis by age and sex. These data are presented in graphic form in charts 1 and 2. Maryland was not included with the Southern States for the reason that its age-sex distribution of tuberculosis mortality for

TABLE 3

Mortality rates per 100,000 population by age and sex for all forms, pulmonary, and other forms of tuberculosis in eleven Southern States and the Registration Area exclusive of the Southern States, 1930–1932

AGE-GROUPS	WHITE						COLORED					
	Male			Female			Male			Female		
	All Forms	Pulmonary	Other Forms	All Forms	Pulmonary	Other Forms	All Forms	Pulmonary	Other Forms	All Forms	Pulmonary	Other Forms
Eleven Southern States												
0–4	14.4	5.1	9.3	14.7	4.9	9.8	35.1	18.8	16.3	32.2	18.4	13.8
5–9	4.1	1.4	2.7	3.8	1.5	2.3	16.2	8.5	7.7	15.9	10.7	5.2
10–14	5.2	2.6	2.6	5.3	3.4	1.9	22.5	16.3	6.2	50.5	44.5	6.0
15–19	16.4	13.1	3.3	29.1	25.8	3.3	110.8	98.6	12.2	182.8	170.8	12.0
20–24	46.8	42.7	4.1	69.9	65.7	4.2	236.8	218.5	18.3	292.0	267.6	24.4
25–29	62.4	57.4	5.0	85.5	81.4	4.1	253.1	234.0	19.1	260.0	241.7	18.3
30–34	76.3	72.4	3.9	86.0	81.0	5.0	275.3	257.7	17.6	250.5	238.2	12.3
35–44	84.2	82.1	2.1	74.6	69.8	4.8	234.7	222.2	12.5	186.7	173.4	13.3
45–54	91.9	84.6	7.3	79.8	73.7	6.2	177.2	164.6	12.6	152.2	142.1	10.1
55–64	123.5	113.8	9.7	110.7	102.5	8.2	166.1	155.4	10.7	140.1	129.3	10.8
65–74	177.3	160.3	17.0	180.9	165.9	15.0	170.8	158.1	12.7	127.0	115.0	12.0
75–	202.5	183.3	19.2	224.4	195.4	29.0	119.0	117.3	1.7	96.5	86.4	10.1
Registration states exclusive of eleven Southern States												
0–4	26.2	7.2	19.0	24.0	6.8	17.2	164.1	78.3	85.8	132.9	63.8	69.2
5–9	7.3	2.3	5.0	6.8	2.4	4.4	69.3	42.0	27.3	45.0	26.9	18.1
10–14	6.2	3.3	2.9	9.9	6.6	3.3	88.5	63.2	25.3	142.2	119.1	23.1
15–19	23.8	20.6	3.2	48.7	43.7	5.0	274.7	238.8	35.9	387.7	353.7	34.0
20–24	57.9	52.5	5.4	91.3	85.2	6.1	350.2	232.9	26.3	412.5	399.8	12.7
25–29	74.7	69.7	5.0	90.1	84.1	6.0	322.5	292.5	30.0	331.6	309.3	21.3
30–34	81.4	75.4	6.0	73.0	68.0	5.0	352.9	322.2	30.7	275.5	249.2	26.3
35–44	98.1	91.7	6.4	58.2	52.9	5.3	341.8	311.9	29.9	224.6	202.4	22.2
45–54	116.9	109.9	7.0	51.3	46.5	5.2	346.9	321.1	25.8	174.7	159.1	15.6
55–64	119.5	111.2	8.3	55.5	49.2	6.3	318.4	293.8	24.6	183.9	164.4	19.5
65–74	117.5	107.9	9.6	77.3	68.6	8.7	403.6	367.9	35.7	204.2	186.2	18.0
75–	101.4	90.4	11.0	88.5	78.9	9.6	367.9	331.5	36.4	213.0	198.3	14.7

white persons was more nearly like that of the Northern than that of the Southern States.

Rather than compare the rates for each age-group tabulated, three main age-groups are used in comparing that of the South with that of

the remainder of the country. The three main age-groups include (1) those under 15 years, (2) those 15 to 45 years and (3) those 45 years and over.

Age-Sex Distribution in White Population

Among white persons under 15 years of age the mortality rates for each sex have been comparatively low in the Southern States as a group.

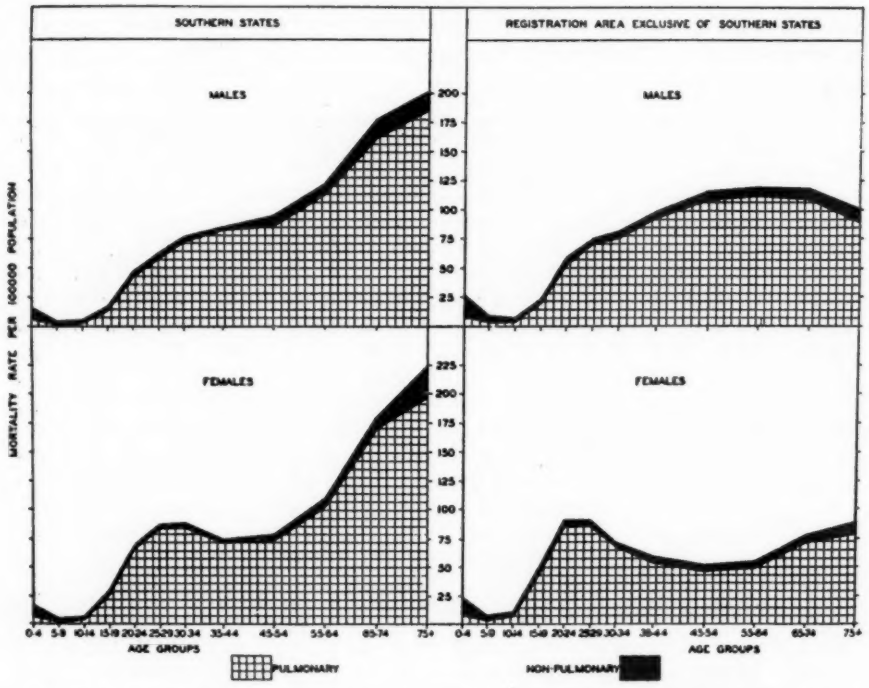


Chart 1. Average annual mortality rates per 100,000 population from pulmonary and nonpulmonary forms of tuberculosis by age and sex among white persons in eleven Southern States and in the Registration Area exclusive of the Southern States, 1930–1932

In Kentucky and Tennessee, however, the rate for this age-group exceeded that for the Registration Area exclusive of the Southern States. In most of the other Southern States the rate has been exceedingly low.

In the age-groups in which the adult type of tuberculosis is said to develop most frequently, that is, between 15 and 45 years, the Southern States as a whole have had lower death-rates than the remainder of the Registration States. However, in each of the States of Tennessee, Kentucky, and Virginia, both sexes have had higher mortality rates.

The greatest variation in mortality of the two areas under consideration has been in the older groups, 45 years of age and over. In the South the rates have tended to increase constantly in each group over 45 years, while they have tended to remain constant or have decreased, depending on the sex, in the remainder of the country. The increased rate in old age in Tennessee, Kentucky and Virginia has been very marked. This characteristic distribution of mortality in old age for both

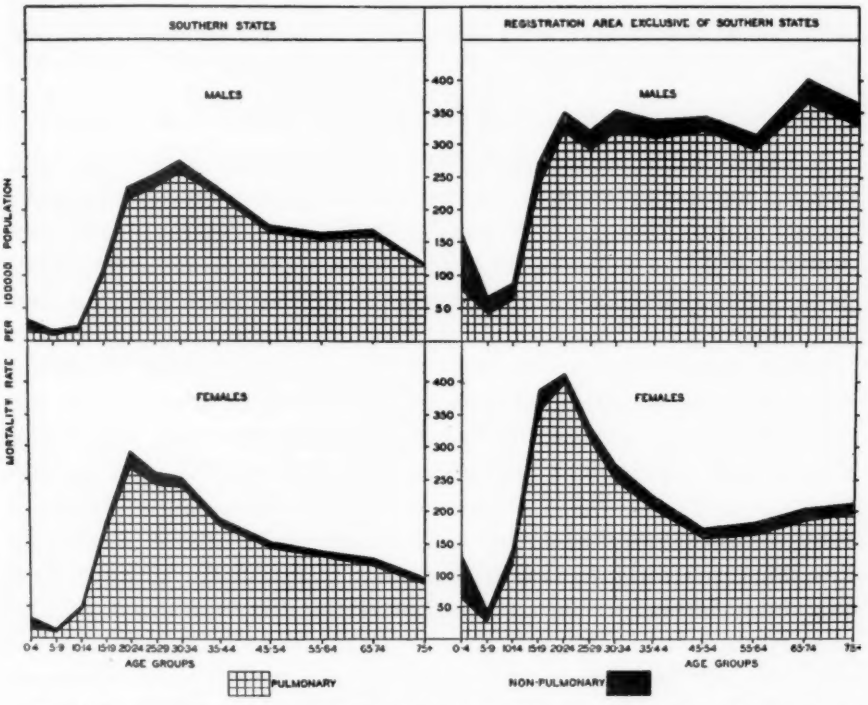


Chart 2. Average annual mortality rates per 100,000 population from pulmonary and nonpulmonary forms of tuberculosis by age and sex among colored persons in eleven Southern States and in the Registration Area exclusive of the Southern States, 1930–1932

sexes in Southern States has, according to the available data, no counterpart for white persons in other countries or parts of the world.

In the Southern States there have been no consistent differences in the age-distribution of mortality for males and females except in the young-adult groups from 15 to 45 years. The rates among females have been consistently higher and the increase has begun earlier in life than among males. In this respect the South has not been different from other parts of the United States.

Age-Sex Distribution in the Colored Population[6]

In the colored population mortality rates have been lower in all age-groups for both sexes in Southern States than those for the rest of the country. In general, the mortality curve for females has been similar in the two areas except for the height to which the rates have risen. In both groups of States the rate has tended to fall in the older ages following the rapid rise in the young-adult group. Among males the rates have tended to decrease in old age in the South, while they have remained at a very high level from young adult life through old age in other parts of the country.

Mortality from Nonpulmonary Forms of Tuberculosis by Age and Sex

Mortality rates from nonpulmonary forms of tuberculosis have been in some respects different in the South from those in other parts of the United States. For the total population the mortality rates have been comparatively low in the South. This difference in rates is not contrary to the usual difference found in mortality for warm and cold climates. (See table 3.)

In the younger age-groups of the white population of the South the rates are lower for both sexes as compared with those for the remainder of the Registration Area. It is interesting to note that tuberculosis among cattle, as reported by the United States Department of Agriculture, has been since 1930 more prevalent in the region bordering on the South Atlantic and Gulf Coasts than in other parts of the South. In this most southerly portion of the country mortality rates for nonpulmonary forms in children have been lower than for the remainder of the area.

In the older ages of the white population, mortality from nonpulmonary tuberculosis has been comparatively high in the South. The increase in the rate in age-groups over 45 years has been consistent in all of the Southern States, and is so to a much less extent in the remainder of the Registration Area.

In the colored population, mortality from nonpulmonary forms has been lower in all age-groups in the South than in the remainder of the

[6] The colored population of the Registration States exclusive of the eleven Southern States is made up of approximately two-thirds Negroes according to the 1930 Census. Most of the remainder are Indians, Mexicans, Japanese and Chinese. Data on mortality from tuberculosis for colored persons in Cleveland, Detroit, Pittsburgh and Cincinnati, and from the State of New Jersey, where the colored population is almost exclusively Negro, indicate that the age-distribution of the Southern States has been similar to that shown for the total colored population of the same area.

Registration States. In the South the rates for colored persons have exceeded those for the whites in all age-groups except among those 65 years of age and over. The rates among colored persons in the Registration Area exclusive of the Southern States have been much higher in all age-groups than among white persons of the same area.

SUMMARY

1. Tuberculosis mortality for white persons has been for a period of years higher in Tennessee and Kentucky than in the Registration Area as a whole. Virginia and Maryland have had rates about equal to those for the entire country. The remainder of the South has had a relatively low rate.

2. Tuberculosis mortality in the colored population has been much lower in the Southern than in the Northern States.

3. In the southeastern section of the country the area of high mortality for the white population centres in Tennessee and Kentucky. It declines gradually in all directions from this central zone. The areas or zones of high mortality for the colored population of the Southeastern States are quite similar in extent to those for the white population.

4. Consideration of available data regarding environmental, social and economic conditions in relation to tuberculosis mortality does not explain satisfactorily the wide variations in mortality for different parts of the Southeastern States.

5. The mortality from tuberculosis, according to age-groups, has shown decided differences in the Southeastern States as compared with the remainder of the Registration Area. The greatest difference was that found in old age. In the Southeastern States the rates for the white population have tended to increase rapidly as age increased for both males and females. In the colored population the rates have been generally higher in the Registration Area exclusive of the Southern States. In this area the rates for colored males have been high throughout adult life and in old age.

6. The mortality from nonpulmonary forms of tuberculosis has been lower in the Southeastern States as a group than for the remainder of the country. However, among white persons the mortality has shown an increase with advancing age, roughly paralleling that for the pulmonary forms of the disease.

7. There is as yet no satisfactory explanation for the wide differences in mortality in different areas of the southeastern part of the United States, nor for the peculiar age-distribution of the mortality.

RESULTS OF THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS IN THE NEGRO

LINCOLN FISHER[1]

This brief report is offered as a possible stimulus to the progress of collapse therapy in a race regarded as possessing relatively poor native resistance to pulmonary tuberculosis. The reasons for this lower resistance are partly biological, and partly economic and sociological, the salient feature being that the tuberculosis death-rate among Negroes remains more than three times the corresponding rate for the white population. The literature on this subject is fairly voluminous and scarcely calls for review in a short paper devoted to the surgical phase. Suffice to summarize, with Pinner and Kasper (1):

> We are impressed by the necessity of considering the likelihood of true genotypic differences between the two races in order to explain their different reactions to tuberculosis. The discrepancies observed lead necessarily to the conclusion that infection tends to produce a high state of allergy in the Negro, but that he, unlike the white, does not readily acquire a state of increased resistance coincidently.

Our present thesis cannot therefore be divorced from the fundamental background of an inferior resistance in the colored race as compared to the white. Nevertheless, we have gradually come to feel that individual response to tuberculous infection and disease may not infrequently be a thing apart from racial trends or customary experience. It requires many generations to develop that ephemeral quality called "resistance" in a race as a whole, but meanwhile certain individuals will stand out a little ahead of the procession, as a higher degree of immunity is gradually developed.

Hitherto, rather scant opportunity has been found to evaluate the results of active treatment of pulmonary tuberculosis in the Negro, in comparison with results obtained generally in all races. To be sure, careful epidemiological and pathological studies have been carried on;

[1] Mansfield, Ohio.

but, as a rule, practically no attempts are being made to compile separately the results of collapse therapy in the Negro, for whom surgical intervention has been infrequently attempted. Many communities, because of their high ratio of Negro population with notably inadequate economic resources, have been unable to provide adequate facilities for sanatorium treatment. Not until rather recently has the National Medical Association (of Negro physicians) succeeded in working effectively, side by side with the National Tuberculosis Association, on essential problems relating to childhood infection. As further coöperation is secured, this basic work must help solve the now urgent problems of exposure, repeated infection and allergy, as related to resistance or immunity. Poor economic status intensifies the difficulties to be met. However, the large number of Negro nurse-girls, maids and food-handlers (both cooks and waiters or waitresses) makes a solution equally imperative from the standpoint of the Caucasian peoples who employ them. The antituberculosis campaign has far-reaching ramifications in congested districts.

There is no question that the average type of disease seen in the Negro is more fulminant, pathologically speaking, and of shorter clinical duration. This more acute tuberculosis, with a tendency to pneumonic consolidation, has usually given symptoms for a briefer period. There may be few or no râles, and the sputum is frequently negative for tubercle bacilli until caseation or excavation has taken place. This may occur extensively in a very short time. Meanwhile, vast numbers of bacilli are poured out for home consumption, so to speak. Child and adolescent contacts are usually numerous and intimate. Heavy seeding of entire families is, in the nature of the case, unavoidable, and the results disastrous. By the time this situation is discovered, it is often too late for effective remediation.

In addition to early diagnosis, we realize to-day the importance of timely collapse therapy. In the Negro, unusual promptness is demanded. Hospitalization prevents further home contacts, but bed-rest is seldom sufficient for permanent cure. Palliative rest being of uncertain advantage, drastic collapse of diseased areas of lung tissue is required. Unfortunately, many Negroes have a tendency to rapid involvement of the hilar, mediastinal and mesenteric lymph nodes; this fulminant, generalized adenopathy assumes really malignant significance in the prognosis. Such extensive lymph-node hypertrophy is rarely seen in white patients. Complications such as intestinal and

laryngeal tuberculosis are likewise more frequently seen in the Negro; unhygienic conditions, lack of properly balanced diet, and perhaps relative ineffectiveness of actinic radiation on heavily pigmented skins, may play a part. The mulatto seems to have acquired some of the Caucasian resistance to tuberculosis, but unfortunately is sometimes less cooperative while under treatment than is the full-blooded Negro.

It has appeared of late that we are probably, more frequently than hitherto, seeing fibrotic lesions in our colored patients. Whether better educational and field-work facilities in our diagnostic clinics have routed out some of the more chronic survivors is difficult to say, but it is slightly encouraging to see, every now and then, in a Negro patient, disease which is definitely comparable to chronic white tuberculosis. The consolidated type of lesion notoriously did badly in the past, even during attempted pneumothorax collapse. Induced diaphragmatic paralysis was only occasionally effective in the Negro. Now we have some ambulatory pneumothorax cases among colored patients, and have had some cases of dramatic arrest of disease by phrenicectomy, sometimes combined with scaleniotomy. However, if artificial pneumothorax can be established satisfactorily, we favor immediate collapse of the lung in suitable Negro patients. Intrapleural pneumolysis has converted inefficient pneumothoraces into effective collapse in suitable cases. Generally speaking, nothing short of early, complete collapse of the diseased lung has proved sufficient in the Negro.

Given a predominantly fibrotic type of lesion, that is, a certain degree of chronicity, there is no apparent reason why the Negro should not benefit from surgical collapse therapy to the same extent as the white patient. After choosing the more comparable types of disease for radical collapse, as indicated, we found the end-results to be comparable, also. Unfortunately, the number of such suitable cases among Negro patients remains relatively small.

We have at our disposal the following measures for relaxation or collapse of the tuberculous lung:

I. Phrenic-nerve interruption
   A. Temporary
      1. Crushing
      2. Alcohol injection (plus resection of all accessory phrenic roots, in either case)
   B. Permanent
      1. Phrenicectomy (evulsion, or resection of at least 12 cm. of nerve, plus resection of accessory roots)

II. Scaleniotomy
  A. Combined with phrenic-nerve interruption
  B. Subsequent to prior phrenic-nerve interruption
  C. Independent

III. Multiple intercostal neurectomy (supplementary to phrenicectomy and scaleniotomy)

IV. Artificial pneumothorax
  A. Intrapleural pneumolysis (supplementary)
    1. Closed (cauterization)
    2. Open (ligation and cutting)
  B. Oleothorax (substituted to prevent obliteration due to adhesive pleuritis)

V. Extrapleural pneumolysis
  A. Paraffin filling
  B. Pedicled muscle implant
  C. Temporary packing
    1. Gauze
    2. Inflatable rubber bag

VI. Extrapleural thoracoplasty
  A. Paravertebral
    1. Partial
    2. Total
  B. Anterolateral (supplementary)

Phrenic-nerve interruption, scaleniotomy and multiple intercostal neurectomy all have as their aim the paralysis of accessory muscles of respiration, namely, the diaphragm, the scalene and the intercostal muscles, respectively. All three methods afford relaxation to the diseased lung, rather than active compression of any specified area of lung tissue. Phrenic-nerve interruption results, according to the method employed, in either temporary or permanent immobilization and more or less elevation of the hemidiaphragm, producing relaxation of the entire elastic pulmonic structure, from base to apex. Section of the scalene muscles, which have their insertions upon the 1st and 2nd ribs, relieves the upper ribs from the bucket-handle lift on each inspiration. The resulting relaxation of the apex impairs, also, the function of the adjacent intercostal muscles. Multiple intercostal neurectomy renders this loss of function more complete.

The ideal therapeutic pneumothorax merely relaxes the lung by neutralizing the customary negative intrapleural pressures. Diseased areas have a tendency to contract first, because of their pathological loss of elasticity. When localized pleural adhesions over the involved

site interfere with satisfactory collapse, the adhesions must be cut, if suitable, under thoracoscopic guidance, with either the galvanocautery or high-frequency electrode, or they may be divided by the open-incision method: the latter is usually attended by more severe reactions, as a result of opening the pleural cavity. Following successful intrapleural pneumolysis by either method, the lung is free to collapse efficiently during subsequent pneumothorax treatment. Oleothorax may be substituted for a partial pneumothorax that is gradually being obliterated by adhesive pleuritis; thus the existing collapse may be maintained by sterile mineral oil injected into the pleural cavity.

Thoracoplasty and all the forms of extrapleural pneumolysis or apicolysis afford more active compression, in addition to a marked degree of relaxation which permits fibrotic contraction from within. It has been suggested that this internal contraction, to some degree, results from kinking or obstruction of the smaller bronchi, attended by atelectasis of the surrounding lung.

Inasmuch as uncomplicated artificial pneumothorax has ceased to be considered a truly surgical procedure, we shall dispense with further mention of it. The end-results of minor surgical measures are more uncertain in the Negro than in the white patient; hence, in the event of an unsatisfactory establishment of artificial pneumothorax, major surgical collapse is generally indicated without unwarranted delay.

There are fewer contraindications to apicolysis than to thoracoplasty. The cavity should not be too large (preferably under 4 cm. in diameter), nor too thick-walled or too nearly subpleural. The dangers are mainly two: infection of the bed of the extrapleural wound, or ulceration and rupture of the paraffin pack into the pulmonary cavity. Muscle implants, although carefully pedicled to preserve the blood-supply, have an unfortunate tendency to atrophy, defeating their purpose. Temporary extrapleural packing with gauze or an inflatable rubber bag has certain obvious disadvantages, but it may often be effective. Any of these forms of plombage may be employed as preliminary, or as supplementary to thoracoplasty, if indicated.

Preferably, certain requirements should be satisfied before thoracoplasty is considered strictly suitable: (1) the patient should be under fifty years of age; (2) the cardiovascular-renal system should be compatible with elective major surgical recommendations; (3) the lesion should be mainly unilateral and predominantly fibrotic (not pneumonic) in type; (4) the mediastinum should be stabilized in the midline, as

evidenced roentgenographically by retraction of the trachea and heart toward the side of prospective rib-resection; (5) the temperature and pulse-rate should have been approximately within normal limits for several months before operation.

Although strict adherence to these ideal requirements may not always be enforced, in the main they must be followed if achievement of good results is to be anticipated. It is a well-recognized corollary of surgical experience that an occasional "poor risk" does unexpectedly well, but the odds against are necessarily great. It must not be overlooked that tuberculosis patients coming to major surgery are already handicapped by a depletion of vital capacity and of cardiovascular tone, attendant upon more or less protracted chronic disease. Especially, in the presence of chronic suppuration such as empyema, amyloid degeneration of the viscera must be looked for.

In the absence of definite contraindications, we prefer thoracoplasty to apicolysis in the treatment of chronic proliferative tuberculosis. One colored woman who had paraffin plombage of 350 gm. in order to close a 4-cm. apical cavity, has remained perfectly well, her sputum bacillus-free for three years, but this is the only instance in which we have performed an apicolysis on a Negro patient. A posterior approach, after resection of 2 cm. of the 4th rib at the angle, was employed in order to dislodge the cavity from the costovertebral gutter and compress it against the anterior chest-wall.

We have seen only 10 colored patients in the last three years, for whom we could whole-heartedly recommend thoracoplasty. Nine of these accepted the operation. One fatality occurred, following a second (lower) stage, in a girl with bilateral disease. One woman intermittently produces a positive sputum, in spite of excellent thoracoplastic collapse, although her cough and expectoration have become negligible and she feels perfectly well. The other 7 patients show complete arrest of their disease, with closure of cavities and persistently negative sputum; all but one have been sent home to lead reasonably normal lives, and this one is nearly ready for discharge. These give every evidence of permanent cure. One patient who, for the time being, refused thoracoplasty, did decidedly well following phrenicectomy and scaleniotomy, a striking result that was scarcely predictable, considering his race and the extent and character of his disease.

A young colored girl, who developed an acute mixed-infection empyema during the course of artificial-pneumothorax treatment, becoming

rapidly wasted and critically ill, was finally subjected to thoracotomy, with the resection of a piece of one rib, after adequate aspiration through a large needle had become impossible. Air-tight, siphon drainage was established and maintained for two months. Her subsequent recovery has been so complete that the originally contemplated thoracoplasty is no longer indicated.

Of the 9 colored thoracoplasty patients, six were women and three were men; four were right-sided, and five left-sided cases. Nineteen thoracoplastic operations were performed on the 9 patients; at the average stage, a rib-resection of 56 cm. was done. Two patients had a single stage (upper), four had two stages, and three had three stages.

The chief criterion in determining the extent of rib-resection necessary to collapse the diseased area is, of course, the appearance of the stereoscopic chest roentgenogram: Bucky diaphragm technique may give additional information concerning cavities which are masked by marked radiopacity. Physical signs are too often misleading to be dependable in estimating the degree of collapse which will prove adequate. By complete resection of the upper ribs, from the transverse processes of the vertebrae to, or including, the costal cartilages, even large apical cavities may be closed by a thorough-going upper-stage thoracoplasty which is "tailored" to suit the individual needs.

The criteria of a technically successful plastic operation are complete closure of pulmonary cavities and freedom of the sputum from tubercle bacilli. Clinical cure naturally implies the permanent loss of subjective symptoms as well. Coincidently, the chest roentgenogram must be

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Fig. 1. (J. J.) Advanced tuberculous infiltration of left lung, with cavitation below clavicle. Sputum highly positive for tubercle bacilli. Artificial pneumothorax unsuccessfully attempted.

Fig. 2. (J. J.) Marked clearing throughout lesion, with closure of cavity, following phrenicectomy and scaleniotomy. Sputum persistently negative. Left hemidiaphragm immobilized and slightly elevated. Disease arrested.

Fig. 3. (M. L.) Tuberculous cavitation, right apex. Sputum positive. Artificial pneumothorax unsuccessful. Prior phrenicectomy failed to close cavity. Right hemidiaphragm considerably elevated.

Fig. 4. (M. L.) Cavity closed following extrapleural paraffin plombage (350 gm.). Sputum persistently negative. Disease arrested.

Fig. 5. (R. R.) Huge upper-lobe cavity, 8 cm. in diameter. Sputum highly positive. Artificial pneumothorax unsuccessful.

Fig. 6. (R. R.) Closure of cavity and practically complete collapse of right lung, following three-stage paravertebral thoracoplasty with total rib-resection of 188 cm. Sputum persistently negative. Disease arrested.

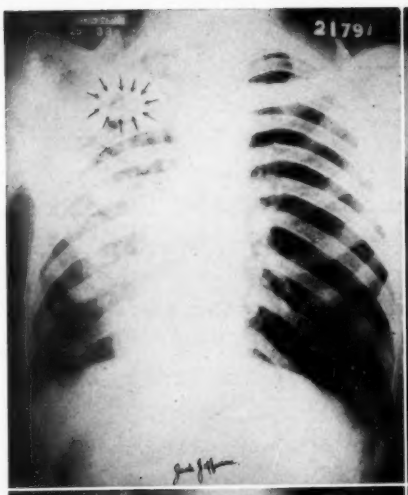


Fig. 1

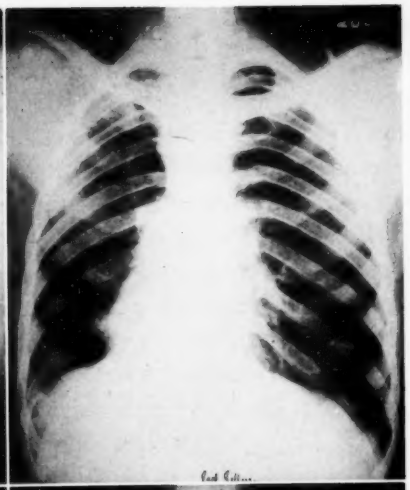


Fig. 2

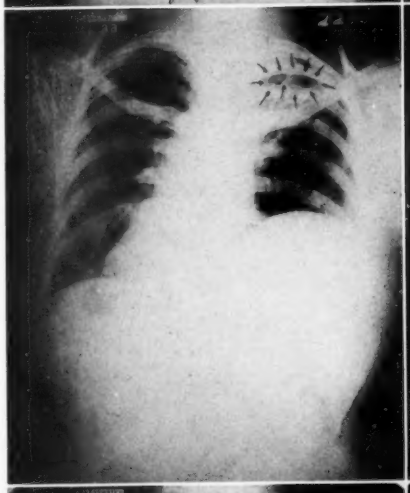


Fig. 3

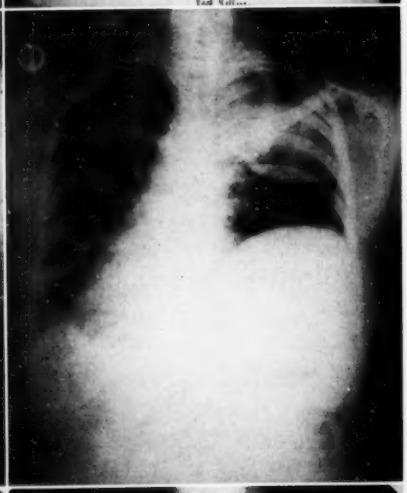


Fig. 4

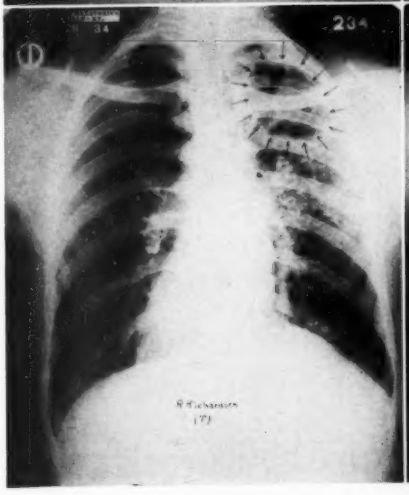


Fig. 5

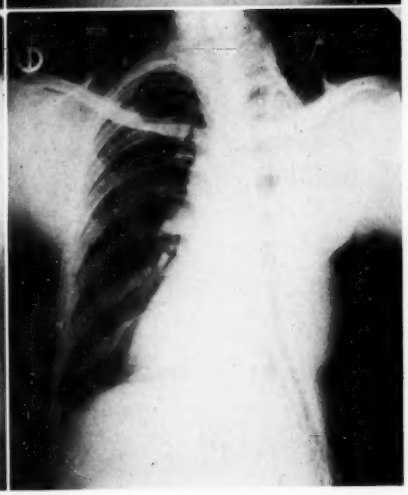


Fig. 6

Figs. 1–5

compatible with arrest of the disease, which, of course, includes the contralateral lung equally with the operated side. Roentgenological changes may be observed for as long as a year postoperatively, although the major improvement usually occurs within the first three months, during which time rib-regeneration appears to become complete. Sometimes it is useful to delay bone-formation by the application of Zenker's solution or formalin to the periosteum at the time of subperiosteal resection. Each patient presents individual problems, rendering actual standardization of procedure impossible and inadvisable.

The X-ray reproductions (figures 1 to 6), included herewith, are representative of the results obtainable in Negro tuberculosis patients, provided only that their disease be potentially fibrotic and pathologically comparable to that found, with much greater frequency, in the white race.

REFERENCE

(1) PINNER, M., AND KASPER, J. A.: Pathological peculiarities of tuberculosis in the American Negro, Amer. Rev. Tuberc., 1932, *24*, 463.

PREGNANCY AND PARTURITION DURING THE COURSE OF BILATERAL ARTIFICIAL PNEUMOTHORAX

With a Report of a Successfully Delivered Case[1]

ANDREW PETERS AND LOWREY F. DAVENPORT

Pregnancy occurring in a patient with pulmonary tuberculosis presents a nice problem as to management, both of the tuberculosis and of the pregnancy. The problem becomes further complicated when some form of collapse therapy has already been undertaken. Yet, one must be prepared for such contingencies, now that various collapse procedures have become increasingly common therapeutic procedures, and be able to give intelligent advice and carry out the most rational procedure in each case, based upon adequate knowledge and accumulated experience, rather than upon obsolete or impractical *obiter dicta*. The case cited here presents an unusual combination of circumstances, and the rarity of their occurrence and juxtaposition in a single individual seem to us sufficient to warrant this report in considerable detail, together with a rather extensive discussion of the pertinent literature and analysis of the different factors to be considered.

GENERAL DISCUSSION OF PULMONARY TUBERCULOSIS AND PREGNANCY

A most comprehensive and excellent review of this subject as a whole is that by Cleaveland Floyd (1) of recent date (1935). This author very effectively points out the changes in viewpoint that have occurred from time to time and how, in the light of modern advances in medical knowledge and its application, the emphasis, from the therapeutic viewpoint, has shifted so as to focus more and more upon the individual tuberculous patient.

It will suffice to pass over very briefly the early period in phthisiology when the opinion prevailed that pregnancy exerted a favorable influence upon the course of pulmonary phthisis in young women. (Franc, Brionde, Dugès (cited by Binet (2)), Sydenham and Baillie (cited by Crocket (3)), and others cited by Fishberg (4) and Bandelier and Roepke (5).)

[1] From the Middlesex County Sanatorium, Waltham, Massachusetts.

Such an opinion may be accounted for by a number of explanations, partly physiological, partly psychological, and partly attributable to limitations of the methods of observation then available. Certainly, such an opinion is not now held by more than a small minority of clinicians; although there are many, such as Barnes and Barnes (6), and Jennings and Mariette (7), who have concluded that the unfavorable effects of intercurrent pregnancy have been exaggerated or cannot be statistically proved. Such conclusions, on the other hand, appear to take too little account of well-authenticated clinical observations and experience, and do not sufficiently distinguish between the factors that affect the balance one way or the other or between the very different sort of material that may be included in different groups studied. Yvonne Binet (2), in a very thoughtful study and discussion, relates that the elder Louis, after much hesistation, became convinced of the bad influence of gestation on phthisis, and that Grisolle in 1849 and Dubreuille in 1852 added their confirmation, which is now contested by few experienced clinicians, while Cullen pointed out that "the symptoms (following temporary amelioration) later return with violence and cause death within a brief period of time." Binet points out, however, that not all tuberculous women react in the same way to pregnancy, that not only do the stage and the "evolution" of the disease process make a difference but also the "reactive state" of the organism, that is, the patient. In her discussion, she speaks especially of the active, caseous forms. While the appearance of a pregnancy in one of these patients demands immediate therapeutic notice, there is, in her opinion, no certain test or measure of "activity." Even the behavior of the tuberculin cutireaction is not constant, and Binet concludes that repeated examinations and serial X-rays are the best way to establish the type of the disease. Decaulne (8) quotes Rist to the effect that "every pregnant woman in whom tuberculosis develops is threatened with death after a brief delay." This sequence is, of course, slightly different from that in which the patient has been already under treatment for tuberculosis and later becomes pregnant, yet Matthews and Bryant (9) concluded in 1930, from a follow-up of 484 female patients discharged from Trudeau Sanatorium, that pregnancy has a distinctly deleterious effect upon the pulmonary disease.

From the above observations and conclusions, it was an easy jump for many minds to the idea that pregnancy should be terminated by active intervention (abortion) whenever encountered in tuberculous

women, and for a time this was established procedure among obstetricians and gynecologists, especially in Germany, and also to a considerable extent in the United States. Pankow (10), in 1926, believed that in cases of "manifest tuberculosis" gravidity should be terminated in the first few months of pregnancy. This qualification as to time has usually been recognized because of the more formidable nature of abortion in the later months and the common observation that under these conditions it almost invariably failed to benefit the mother while it sacrificed the child. Forssner, Sundell and Kjellin (11), in 1924, reported a very careful survey of the literature then available and also of the out-patients of two large maternity institutions of Stockholm. They found among the pregnant and nonpregnant groups, subdivided according to stage of the disease, of women of 17 to 40 attending the Dispensary of the South of Stockholm, and excluding "cured" cases of tuberculosis, less than 10 per cent difference in results between any two comparable groups (pregnant and nonpregnant), and that chiefly in stage-III cases. As to the results achieved by abortion, they quote directly from the German statistics of Pankow and Kupferle and of Krönig's clinic, and conclude that no proof had been furnished that abortion checks the active evolution of the tuberculous process; the results in stages II and III have not been satisfactory, while stage-I cases generally go through pregnancy and labor without harm. Hence, the occasion for inducing abortion should be rare. Glaser (12), in an admirable review in 1933, practically confirms them regarding the unfavorable results in tuberculous patients who were aborted; and both he and Roloff (13) believe that collapse therapy has removed the necessity for this in most cases, also decrying its practice as needless destruction of the foetus without assurance of compensatory benefit to the mother.

RÔLE OF PNEUMOTHORAX THERAPY

Roloff (13) credits Forlanini with reporting the first case of pregnancy occurring during the course of therapeutic pneumothorax. This observation was published in 1906, in the *Deutsche mediziner Wochenschrift*, occurring in the second case therein reported, of a patient who became pregnant eighteen months after the institution of pneumothorax treatment, and went through a normal pregnancy still carrying her pneumothorax, remaining well; and Forlanini subsequently informed Van Voornveld that she had passed successfully through another pregnancy and delivery. The pneumothorax, of course, was on one side

only, as bilateral pneumothorax was not then practised. According to the same author (Roloff), Spengler and Neumann, in 1913, described a pregnancy with subsequent establishment of a pneumothorax, and in 1917 Van Voornveld advocated this mode of treatment, closely followed by Unverricht and Hegler. Rist (14), who has already been quoted, was among the first in France (1921) to advocate pneumothorax therapy in tuberculous women who become pregnant. After observing that whether abortion increases the chance of improvement is doubtful, he said that "where the pneumothorax is unilateral a pneumothorax should be done and that in a number of such cases, a living child was born and the mother remained well." Decaulne, already cited, reviewed in 1926 the results in 5 cases of pulmonary tuberculosis treated by pneumothorax before pregnancy (under Pellé) of which three did well, and 9 cases in which this treatment was begun during pregnancy, including four observed and recorded by Rist (1914), Réal (1914), Van Voornveld (1917), and Slater (1918), adding 5 cases personally observed. His report was quite favorable, and he stated that the cases had been followed up. The following year (1927) Pierre Andler (15) reported a considerably larger group of women cared for on Rist's service or that of Couvelaire, from Paris and vicinity. His figures covering 52 cases in which tuberculosis antedated gestation and pneumothorax was impossible or not carried on, were shockingly unfavorable, 82.6 per cent being made worse after gestation and 36.5 per cent dying within a year. The group of pneumothorax-treated cases comprised fifty-six, in twenty-five of which pneumothorax was established before or during gestation and in thirty-one of which pulmonary tuberculosis antedated gestation. His many subgroupings make the figures difficult to grasp, but he reached the conclusion that both the female reproductive function and the practice of therapeutic abortion worsened the prognosis in the tuberculous patient, while artificial pneumothorax was the procedure of choice, yielding nearly 60 per cent good results when tuberculosis preceded gestation and 40 per cent when it appeared at the beginning of gestation or during it. Andler found bilateralization of the disease the gravest complication. At that time bilateral pneumothorax was practised sparingly, but in one of the cases described by Andler, a young woman of 21, in whom the onset of clinical tuberculosis coincided with gestation, consecutive bilateral pneumothorax was done with excellent results (1925 and 1926). In another case gestation occurred between two alternate pneumothoraces. Sergent (16), in 1926, advocated it

following delivery in order to counteract the rapid descent of the diaphragm and reported 5 cases in which it was so employed.

The coincidence of pregnancy and bilateral pneumothorax is obviously of rather rare occurrence, although, since bilateral pneumothorax has achieved more favor as a therapeutic measure and is employed much more commonly and earlier in the course of active pulmonary tuberculosis than formerly, it is rather surprising that not more cases of such a coincidence have been recorded, whether of pregnancy as an unwanted or accidental complication, or of such a pneumothorax induced to treat an already existing case of pulmonary tuberculosis in a pregnant patient.

We believe that priority in the recording of such a conjunction of events belongs either to Andler (cited above) or to Rist and Coulaud (17) who, in a report of date April 13, 1929 and finally published in June, 1929, described the case of a young woman journalist with pulmonary tuberculosis, who had had a bilateral therapeutic pneumothorax, on the second (left) side instituted in September, 1927. In the following November the existence of pregnancy was determined at the Baudelocque Maternity Clinic, but the woman refused further hospitalization until just before term. This patient apparently had a traumatic perforation of the right lung following a refill, but was nevertheless successfully delivered ten days later and did well, returning to her work against advice in October, 1928, but continuing pneumothorax refills as an ambulant patient.

Shortly after this, a similar case was reported by Triboulet and Valtis (18), whose case of pregnancy was noted in July, 1928, and admitted later to the Hôpital Laennec, Paris, and delivered at the Maternité Baudelocque in April, 1929, without untoward incident.

Roloff (19), in August 1929, also reported from Ulrici's service at Charlottenburg, Germany, a case which he then believed to be the first of pregnancy and delivery occurring in the course of bilateral-pneumothorax treatment. This was of a young woman of twenty years, and delivery occurred April 1, 1929. A right phrenicectomy was subsequently performed in this case, as pneumothorax on this side had to be abandoned following an exudate.

As far as we can determine the only similar case-report published to date in the English language is that of Duryea (20) from Honolulu. The patient, a part-Hawaiian singer and dancer, became ill with a rather acute type of pulmonary tuberculosis in 1930, had bilateral-pneumo-

thorax treatment instituted in September, and was successfully delivered, December 8, 1930, after being in a grave condition during labor. Shortly afterward, a bilateral phrenicoexairesis was done, and the title of the paper draws attention to this aspect rather than to the pneumothorax.

In addition to these 4 (or 5) cases, to which we have referred in some detail, the following have been reported:

Blisnjanskaya (21): Three cases, reported in 1931, of bilateral pneumothorax, pregnancy and delivery of normal child.

Frischbier (22): One case, reported in 1932, of pregnancy occurring in the course of bilateral-pneumothorax therapy with forceps delivery and favorable result.

Vercesi (23): One case of bilateral pneumothorax with pregnancy, reported in 1932, in which delivery was premature.

Sokolovskaya (24): One case, reported in 1932, from Russia, delivered at the Hospital Ostroumova in March, 1931. Bilateral pneumothorax was begun after three months of pregnancy, after abortion had been considered. In this case, the patient nursed the child, which was vaccinated with BCG.

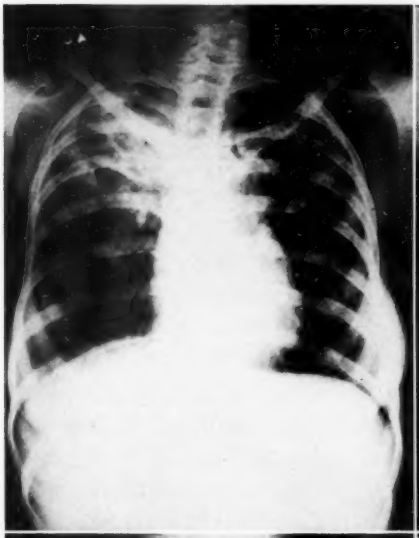
Binet (2): Four case-reports of patients treated by bilateral pneumothorax, who became pregnant and were delivered, with good immediate results. Five case-reports of patients treated by bilateral pneumothorax, who became pregnant and had therapeutic abortion. The immediate results were also good, but all were favorable cases.

Migliavacca (25): Two cases of pregnancy and delivery, with simultaneous bilateral pneumothorax.

To the foregoing, we wish to add the following case, of a patient observed at the Middlesex County Sanatorium, Waltham, Massachusetts, and followed over a considerable period after her delivery, which took place at the Somerville Hospital. She was also seen by Dr. Moses J. Stone, of Boston, who gave her several pneumothorax refills about the time of her confinement.

J. M. K. (M.C.S. no. 7): A 22-year-old married housewife, admitted to Middlesex County Sanatorium, September 30, 1931. *Family history:* Noncontributory. *Past history:* Measles in childhood; whooping cough; and later chorea at 8 years. Married four years. One pregnancy of full-term child, who died at six months of pneumonia (?). *Present illness:* At 10 years patient had attack of pleurisy on left side lasting about one week without known sequelae. In August, 1929, following birth of first child, noticed fatigue on exertion. In November, 1929, had slight afternoon fever, accompanied by cough and sputum: sputum found positive in March, 1930; and in April, 1930, patient was admitted to Central New England Sanatorium. Right artificial pneumo-

Fig. 1



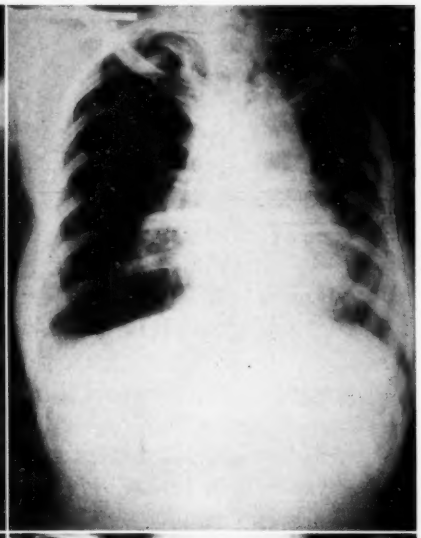
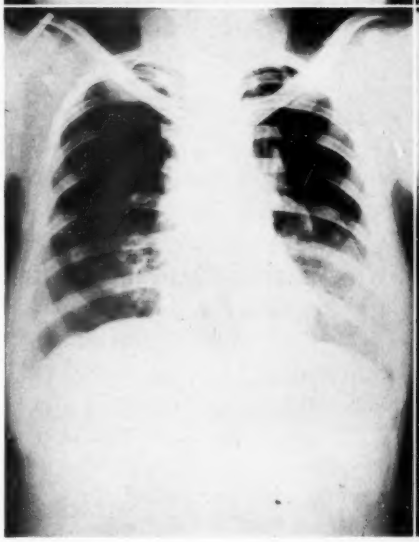


Fig. 2

Fig. 3



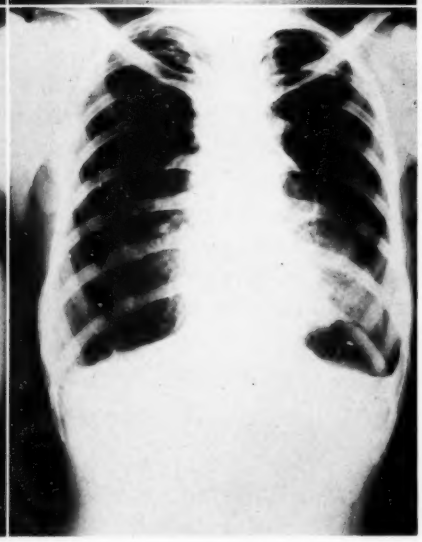


Fig. 4

Figs. 1–4

Fig. 1. X-ray of patient, J. K., taken September 9, 1931, at time of her admission to Central New England Sanatorium

Fig. 2. A film taken December 3, 1931, showing spread of disease on left, leading to institution of bilateral pneumothorax

Fig. 3. Film taken July 19, 1934, just prior to delivery

Fig. 4. Film taken January 16, 1936, showing bilateral pneumothorax with incomplete collapse of large cavity on left

thorax begun, October, 1930, and continued until transfer to Middlesex County Sanatorium, where, on admission, there was slight cough with 2 ounces of sputum daily. *Physical examination:* Well-developed, moderately well-nourished woman, not appearing ill: slight curving of nails: chief findings in chest, where signs of pneumothorax on right and infiltration of upper half of left lung: laryngoscopy showed injection and thickening without ulceration. *Laboratory findings:* Sputum strongly positive on admission and remaining so throughout entire period of observation. Complete blood-count on two occasions within normal limits. Blood-Wassermann negative. X-ray, October 3, 1931, showed incomplete pneumothorax on right of about 60 per cent, with only partial collapse of apex; on left, extensive mottling over upper half of lung field. *Course in hospital:* Irregular febrile course: serial X-rays indicated slight progression of disease on left: accordingly, May 14, 1932, left pneumothorax begun with 250 cc. of air. Refills of bilateral pneumothorax continued approximately weekly. General condition improved, with gain from 115 lbs. on admission to 122½ in July, 1933. On July 1, 1933, patient discharged at own request, to continue rest regimen at home and to return regularly for refills of the bilateral pneumothorax. *Further observations:* Patient under regular observation in our Out-Patient Department since discharge, returning for refills of bilateral pneumothorax every ten days to two weeks. Continued to cough: 1 to 2 ounces of sputum, persistently positive: weight decreased to 109 lbs. in March, 1934, when routine X-ray showed marked elevation of diaphragm, and patient was again admitted, being nearly five months pregnant in spite of medical advice as to dangers of child-bearing. Refills of pneumothorax continued: and on August 4, 1934, patient was admitted to Somerville Hospital in labor. Two days previously, on August 2, the usual refill of 600 cc. was introduced into the right chest. After a short labor, patient delivered spontaneously of a normal female infant, weight 7 lbs., 10 oz. Immediate course after delivery uneventful, and patient afebrile postpartum. On August 9, 1934, received refill of 500 cc. on left, with initial pressure, −7, −12, and final pressure, 0, −4. Discharged to home, August 11, 1934; and on August 16, 1934, received 600 cc. in right chest at home: pressure readings not recorded. Child immediately placed on bottle-feeding; but mother has persistently refused, in spite of her positive sputum, to consider placing child in foster-home. She returned to Out-Patient Clinic, August 23, 1934, for refill of left pneumothorax, and refills have been continued to date. On April 15, 1935, examination in Out-Patient Department showed a well-developed, markedly undernourished woman of 92 lbs. Reëxamination of chest disclosed signs of incomplete pneumothorax bilaterally. Patient has refused readmission to Sanatorium, and continues to supervise care of infant at home. Is returning at approximately 18-day intervals for bilateral simultaneous refills averaging about 500 cc. each. At last sputum examination, August, 1935, a count of Gaffky-III

on concentrated specimen. Early readmission and discontinuance of right pneumothorax are contemplated.

COMMENT

Several features of particular interest are exemplified in this case. The patient's prognosis, on admission to the sanatorium and during most of her stay, was considered unfavorable because the disease had spread considerably in the left lung while the right was being collapsed by pneumothorax and because an entirely satisfactory collapse on the right had not been achieved after a considerable period of treatment and positive sputum and febrile exacerbations persisted. It was with some trepidation that the decision to induce pneumothorax on the left side was made, and the patient's early reactions following insufflations were such as to increase this trepidation, marked dyspnoea being a noteworthy symptom. The improvement in the patient's condition after the bilateral pneumothorax was established was striking and continued practically up to the time of occurrence of the pregnancy. That she passed through this ordeal with so little extraordinary disturbance seems surprising under the circumstances. That her condition deteriorated later, in view of her insistence on continuing household duties and care of the infant, was in no wise unexpected. On reflection, it seems almost incredible that she should still be living, and her course evidences the tenacity with which life often still continues under enormous physical handicaps.

DISCUSSION

From the cases cited and the observations made on pulmonary tuberculosis, therapeutic pneumothorax and pregnancy, it seems self-evident that some revision and clarification of ideas and procedures is indicated. It seems obvious that the occurrence of pregnancy in the course of pneumothorax therapy, whether this be unilateral or bilateral, is no reason for desisting from such treatment, but quite the contrary; and that often pneumothorax therapy should be instituted when pregnancy occurs in a phthisical patient, or when pulmonary tuberculosis develops in a pregnant woman. Pneumothorax therapy is not a substitute for such well-known effective measures as rest, proper care and proper nourishment; but it supplements them and makes them effective in cases in which they otherwise might fail. This is perhaps a truism, but it applies especially to cases in which the balance is delicate and may be readily

turned one way or the other, as when pregnancy coexists with a recent or unstable tuberculous pulmonary lesion.

Instead of thinking first of interruption of the pregnancy, we should, in the light of past experience, think first of the proper treatment and care of the tuberculous pregnant woman, as Rist, Barnes, Floyd, and many others have aptly emphasized. Binet has well said that no fixed rules can be laid down regarding the interruption of pregnancy in tuberculous patients, and she has shown that the simple fact of interrupting pregnancy, when properly done at a suitable time, does not in itself compromise the future. However, it is generally agreed that therapeutic abortion is contraindicated after the fourth month of pregnancy. We will not discuss here the question of prophylaxis, or contraceptive precautions, highly important as it is, because it has no direct bearing on a case that already confronts us, such as those just reviewed. Neither shall we attempt to discuss the economic ramifications of the question of pulmonary tuberculosis and pregnancy, highly important as they are, and, no doubt, often sufficient to influence a decision as to the proper procedures.

Finally, we must, as careful and conscientious observers, admit, as does Binet, that in some patients pneumothorax therapy is entirely ineffective. However, in these, therapeutic abortion is equally ineffective, and the outcome is fatal in any event.

SUMMARY AND CONCLUSIONS

1. A young woman with advanced bilateral pulmonary tuberculosis, who improved markedly under bilateral-pneumothorax therapy, successfully passed through pregnancy and was delivered of a normal child while continuing treatment. So far as can be determined, there has been only one similar case reported in English, but there are recorded 15 (or 16) cases in foreign medical literature, chiefly French, German, Italian and Russian.

2. Patients in whom a pneumothorax, whether unilateral or bilateral, is well established, tolerate pregnancy and parturition surprisingly well. Pneumothorax therapy should never be discontinued because of an intercurrent pregnancy, but should be carefully continued. It should always be considered, among other therapeutic measures, in pregnant women with pulmonary tuberculosis. In the presence of active progressive lesions it is more often indicated than is therapeutic abortion. In some cases both procedures may be advisable, and the order and

manner in which they are to be carried out demand careful consideration and coöperation between phthisiologist and obstetrician.

3. The estimation of the end-results of any procedure in pulmonary tuberculosis requires careful and repeated observations (and comparisons) over a prolonged period. The problems involved in consideration of pulmonary tuberculosis and pregnancy are manifold and complex and too arbitrary pronouncements should be avoided.

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BLOOD STUDIES IN THE SELECTION OF CASES OF PULMONARY TUBERCULOSIS FOR THORACOPLASTY[1,2]

GULLI LINDH MULLER[3]

The first case of thoracoplasty at the Rutland State Sanatorium was performed in 1927. In reviewing the records of the first patients, it was apparent that only good chronic and quiescent cases, as a rule, were then selected for operation. However, among a group of five operated upon during 1928, one reacted so poorly to the removal of two ribs that the surgical program was abandoned. This patient died six months later from a reactivation of his disease and its extension in the contralateral lung, which at the time of operation showed no roentgenological change from that on admission. His record revealed that there were symptoms of clinical activity during the last few months preceding operation, as indicated by rare night-sweats, fever and rapid pulse. This case is cited to illustrate that patients with symptoms of activity do not as a rule react well to the operation.

Similar experiences have probably occurred in many sanatoria, and it is now generally conceded that thoracoplasty should rarely, if ever, be used during acute, progressive stages of the disease. Its chief application is in the patient who has shown an adequate resistance and in whom extension of the disease has ceased.

In selecting the patient, therefore, certain well-defined indications are now generally adhered to, and the appropriate surgical measures are instituted at the seemingly opportune moment. Among the accepted indices of the patient's resistance and the progress of the disease, we have serial X-rays, the temperature, the pulse and the weight-curves. These factors are now carefully considered in order to prevent such distressing results as are often observed when surgery has been used

[1] Presented before the Pathological Section of the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

[2] Read at a meeting of the Eastern Section of the American Sanatorium Association, Rochester, New York, and the Trudeau Society of Boston, Rutland, Massachusetts, October, 1935.

[3] Rutland State Sanatorium, Rutland, Massachusetts.

when the patient's resistance was low. The success of thoracoplasty accordingly depends, not on the selection of the suitable patient alone, but also on the selection of the time for operation, at a period when the defense mechanisms, tending to control and limit the particular patient's disease, are at their best.

In spite of the realization and adherence to the above principles in the selection of patients with pulmonary tuberculosis for thoracoplasty, a fair number do not obtain the expected benefit from the operation, and some are made definitely worse. The changing technique of the operation promises to eliminate some of the failures due to inadequate collapse; but, at the same time, an improvement in judging activity of the tuberculous process may well avoid certain unfavorable results. Therefore our methods for judging activity should be refined, and, if possible, more accurate measures found for ascertaining that indefinable something called *resistance.*

The careful selection of the patient, using all means available in estimating the probability of the success of a thoracoplasty, becomes even more important when we consider the rapid increase of the number of patients receiving this therapy. As an example, one may cite that at Rutland State Sanatorium, where in 1927 only 0.2 per cent of all patients admitted had thoracoplasty, in 1935 the number will approximate 12 per cent of the admissions. This increase in less than eight years, as well as the age-distribution and the clinical evaluation of the patient's condition and resistance as indicated by the prognosis, is illustrated in chart 1.

As a part of and as a continuation of the studies pertaining to the blood and blood-forming organs in tuberculosis, which we began in 1933 and which include all the patients admitted at Rutland State Sanatorium, a group of thoracoplasties have been selected for this paper. The purpose of these examinations, apart from their purely scientific interest, is to find out, in general, whether any reliable and practical aid can be obtained for the evaluation of activity and, possibly, resistance in the patient with pulmonary tuberculosis, and, specifically in this paper, whether the serial study of the pathological process, as revealed by the abnormality of the peripheral blood, will give any practical aid in the selection of patients for thoracoplasty.

All the blood examinations were made on the venous blood, using standard, accepted procedures with apparatus checked by the Bureau of Standards when available. In this paper we will consider only

the total leucocyte count and the differential, using a modification of Arneth's classification of the polymorphonuclear cells, and the sedimentation rate of the red cells. The sedimentation rate was determined in Rourke tubes with potassium oxalate as the anticoagulant. Corrections have been made for the haematocrit and the results are expressed in millimetres per minute.

From the year 1927 to July 1, 1935, 107 cases have had thoracoplasty. Blood studies were available in 54 patients, seven of whom had em-

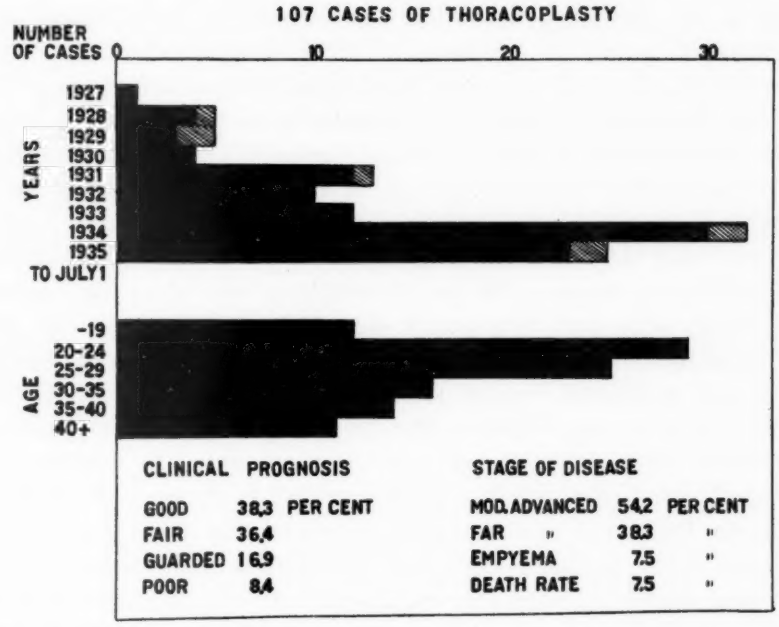

CHART 1. The age-distribution, clinical prognosis and stage of the disease in 107 cases of thoracoplasty. The shaded areas represent the number of deaths. The immediate postoperative mortality was 5.6 per cent.

pyema, with bronchopleural fistula in four. The empyema cases, presenting a somewhat different problem, will be considered separately. In the selection of the patients the usual, well-standardized indications for thoracoplasty were adhered to and will not be discussed in this paper.

To facilitate the presentation of a group of cases, the leucocytic index of Medlar has been employed for two reasons, namely, for its simplicity, and also to discover how far the leucocytic index, alone and in conjunction with the sedimentation rate and the shift to the left of the neutro-

philes, actually represents a working concept that can be applied clinically to measure the activity of the disease. The leucocytic index, ranging from 0 to 100,[4] expresses in one single figure four of the factors in the examination of the leucocytes, namely, the total leucocyte count, and the percentages of polymorphonuclears, lymphocytes and monocytes. It thus considers all the cell types that play a part in the tuberculous process, namely, the monocyte, the importance of which in tubercle-formation has been emphasized by experimental studies of Cunningham, Sabin and co-workers (1), the lymphocytes, the increase of which in the peripheral blood has been shown by Cunningham and associates (2) to indicate resistance or the healing of tubercle, and the polymorphonuclear cell, the chief participant in abscess-formation (3). The derivation and pathological interpretation of this leucocytic index has been described by Crawford (4) and Medlar (5). According to their interpretation, the lower the numerical value of the index the more favorable is the pathological nature of the tuberculous process.

In analyzing the cases, two groups of data have been used, namely, the blood examinations prior to thoracoplasty and those six months after it. In using only two sets of data derived at fixed periods, the significance of the trend of the pathological process before the operation is not considered, but by this method cases can be classified in groups. It is evident, however, that, in most patients over a period of time, shifts occur within the group or from one group to another.

Accordingly, 47 patients have been classified on the basis of Medlar's leucocytic index, the sedimentation rate and the clinical prognosis representing the clinical judgment of the medical staff. These factors have been correlated with the stage of the disease as determined by X-ray films, tubercle bacilli in the sputum, and the haematological and clinical status six months after operation. In deciding whether the patient had benefited from the operation all the data available except the blood examination were considered, and this judgment represents the opinion of the clinical staff.

Table 1 shows 47 patients classified, according to Medlar's leucocytic index, in four groups. It is striking that, when classified in this manner, the smallest number of cases falls into the favorable group and the larg-

[4] Medlar's interpretation of the pathological significance of the leucocytic index is expressed by groups of indices as follows: 0–5, very favorable; 6–15, favorable; 16–21, slightly favorable; 22–26, slightly unfavorable; 27–35, unfavorable; and 36+, very unfavorable. To simplify tabulation, this paper uses the index from 0–15 and 16–26 instead of a subdivision into two groups.

est number into the very unfavorable group. From table 1, it is clear that no correlation exists between the leucocytic index and the extent of the roentgenographic pathological involvement. Before operation tubercle bacilli were found in the sputum in 91.5 per cent of the patients, distributed as indicated in the table. Six months after operation, 51

TABLE 1

The leucocytic index (Medlar) in 47 cases of thoracoplasty

HAEMATOLOGICAL GROUP OR LEUCOCYTIC INDEX NUMBER	ALL CASES	STAGE OF DISEASE		TUBERCLE BACILLI IN THE SPUTUM				UNIMPROVED SIX MONTHS AFTER OPERATION				DIED POSTOPERATIVELY	
		II	III	Before operation		Six months after operation		Haematologically		Clinically			
					per cent		*per cent*		*per cent*		*per cent*		*per cent*
Total before operation	47	28	19	43	91.5	24	51*	13	27.6	11	23.4	1	2.1
0– 15	4	1	3	3	75	0	0	0	0	0	0		
16– 26	15	11	4	13	86.6	6	40	5	33.3	3	20		
27– 35	11	4	7	11	100	4	36.3	3	27.2	1	9	1	9
36–100+	17	12	5	16	94.1	14	82.3	5	29.4	7	41.1		
Total six months after operation	46	28	18	42	91.3	24	52.1	13	28.2	11	23.9		
0– 15	14	7	7	12	85.7	1	7.1	0	0	0	0		
16– 26	13	7	6	12	92.3	7	53.8	2	15.3	2	15.3		
27– 35	7	6	1	7	100	6	85.7	4	57.1	3	42.8		
36–100+	12	8	4	11	91.6	10	83.3	7	58.3	6	50.0		

* These tables would require correction to afford a fair picture of the efficacy of thoracoplasty as a therapeutic procedure. The 51 per cent of cases reported as having tubercle bacilli in the sputum six months after operation includes (1) patients who have subsequently become negative; (2) patients with open bilateral lesions in whom only one side has been collapsed; (3) patients in whom a limited collapse was obtained and further surgery is contemplated at a later date; (4) patients in whom a limited operation was performed and the surgical program interrupted because of an unfavorable reaction on the part of the patient; and (5) patients for whom the goal of a limited procedure was the control of haemorrhage or the reduction of cough and sputum, it being recognized that a bilateral lesion precluded the likelihood of obtaining a negative sputum.

per cent of the cases continued to have tubercle bacilli in their sputum, while the remainder, on repeated examinations, showed none at any time after operation. The percentage of those remaining positive for tubercle bacilli increased from zero in the favorable group to 82.3 per cent in the very unfavorable group. In the favorable group all patients improved both clinically and haematologically, although the clinical

prognosis of these four cases was good in one, poor in one, and fair in two. About one-third of the patients were unimproved haematologically in the other groups; clinically 20 and 9 per cent, respectively, in the intermediate and unfavorable groups; and 41.1 per cent in the very unfavorable group.

Reclassifying the patients six months after operation, a considerable shift was observed. Instead of 4 patients in the favorable group, there were now 14 all clinically improved and with only one patient showing tubercle bacilli in the sputum. After the reclassification, the percentage

TABLE 2

The rate of sedimentation in 47 cases of thoracoplasty

SEDIMENTATION RATE IN MM. PER MINUTE	ALL CASES	STAGE OF DISEASE		TUBERCLE BACILLI IN SPUTUM				UNIMPROVED SIX MONTHS AFTER OPERATION				DIED POSTOPERATIVELY	
		II	III	Before operation		Six months after operation		Haematologically		Clinically			
					per cent		*per cent*		*per cent*		*per cent*		*per cent*
Total before operation	47	28	19	43	91.5	24	51	13	27.6	11	23.4	1	2.1
–0.5	8	6	2	6	75	1	12.5	0	0	0	0		
0.5–1.0	23	15	8	21	91.3	11	47.8	4	17.4	6	26		
1.0–1.5	12	6	6	12	100	10	83.3	7	58.3	4	33.3	1	8.3
1.5–2.0	4	1	3	4	100	2	50.0	2	50.0	1	25.0		
Total six months after operation	46	28	18	42	91.3	24	52.1	13	28.2	11	23.9		
–0.5	21	12	9	19	90.4	5	23.8	0	0	2	9.5		
0.5–1.0	13	11	2	12	92.3	9	69.2	4	30.7	4	30.7		
1.0–1.5	6	3	3	6	100	4	66.6	4	66.6	1	16.6		
1.5–2.0	6	2	4	5	83.3	6	100	5	83.3	4	66.6		

of cases with bacillary sputum and unimproved, both clinically and haematologically, increased progressively from the favorable to the very unfavorable group.

In table 2 the patients have likewise been classified in groups according to the rate of sedimentation in millimetres per minute. This division is arbitrary, and does not represent an actual correlation of the rate of sedimentation to the disease process as based on experimental or clinical analysis. However, all the cases in the group with a rate of 0.5 mm. per minute or less, may be considered as having practically normal or only slightly increased sedimentation rates. It is evident from

table 2 that very few patients selected for thoracoplasty had rates above 1.5 mm. per minute, and these might with advantage have been included in the 3rd group. For convenience in correlation, however, they were divided into four groups.

In general, the same correlation with regard to the stage of the disease, the presence of tubercle bacilli in the sputum and haematological and

TABLE 3

Correlation of the sedimentation rate and the leucocytic index before the operation with the haematological and clinical status six months after the operation in 47 cases of thoracoplasty

HAEMATOLOGICAL GROUP OR LEUCOCYTIC INDEX NUMBER	NUMBER OF CASES	SEDIMENTATION RATE IN MM. PER MINUTE				SIX MONTHS AFTER OPERATION			
							Unimproved		
		-0.5	0.5–1.0	1.0–1.5	1.5–2.0	Tubercle bacilli in sputum	Haematologically	Clinically	Clinically and haematologically
						per cent	*per cent*	*per cent*	*per cent*
Number of cases before operation	47	8	23	12	4	51	27.6	23.4	17
0– 15	4	1	3			0	0	0	0
16– 26	15	3	9	3		40	33.3	20	20
27– 35	11	1	3	4	3	36.3	27.2	9	9
36–100+	17	3	8	5	1	82.3	29.4	41.1	17.6
Six months after operation: tubercle bacilli in sputum		12.5	47.8	83.3	50				
Unimproved:									
Haematologically		0	17.4	58.3	50				
Clinically		0	26	33.3	25				
Clinically and haematologically		0	8.6	33.3	25				

clinical improvement after operation exists in these groups as in those classified according to the leucocytic index. After reclassification six months later, there is a discrepancy between the number haematologically and clinically unimproved. Among those in the group with a sedimentation rate of 0.5 mm. per minute or less, two are clinically unimproved six months after operation. Subsequently both of these have shown marked clinical improvement. Also, in the group with a sedimentation rate above 1.0 mm. per minute six months after opera-

tion there was a greater number who did not improve haematologically than clinically. This is of significance in the light of subsequent events in the course of the disease of some of these patients who have been observed for longer than 6 months. One of these is now losing weight and has gastrointestinal symptoms, another who was discharged is now advised to reënter the sanatorium, and one has had additional surgery, while one, considered well enough clinically to become ambulatory, has not to date (one year after operation) shown any haematological improvement.

In tables 1 and 2, both the leucocytic index and the sedimentation rate show a considerable correlation with the clinical results after operation. The question therefore arises, whether the leucocytic index and the sedimentation rate do not give the same information. This would be true, at least partially, if these two factors ran parallel, that is, if all the cases in the favorable range, according to the leucocytic index, showed practically normal sedimentation rates. This does not occur, however, as may be seen from table 3 in which the leucocytic index has been correlated with the sedimentation rate. It is evident that a practically normal sedimentation rate may be found in a patient with a favorable as well as a very unfavorable leucocytic index and that the sedimentation rates in these latter cases give more reliable information as to the status of the patient. Also, in the group with a slightly favorable or unfavorable leucocytic index (range 16–26), in which the outlook might be considered at least fair, three cases with a sedimentation rate between 1.0 and 1.5 mm. per minute and, in addition, with an increase in the band forms or a shift to the left of the neutrophiles before operation were not only both clinically and haematologically unimproved by the operation, but made definitely worse. Is this only a coincidence in the small series of thoracoplasties here presented? Also, is it a coincidence that among those with a practically normal sedimentation rate only one case, although clinically improved, has bacillary sputum after the operation and that this patient had a very unfavorable leucocytic index?

Of the cases with Arneth counts available before operation, ten had an increase of the band forms, or a shift to the left of the neutrophiles. Of these, 90 per cent had tubercle bacilli in the sputum six months after operation, and 80 per cent were haematologically unimproved, while 50 per cent showed no clinical improvement. Some of those classified as haematologically unimproved in this group but clinically improved

have subsequently shown that the clinical improvement was more apparent than real.

In preceding tables the haematological facts about patients who have had thoracoplasty have been considered. In table 4 the clinical evaluation of the patients before operation, as represented by the prognosis, has been correlated with the same factors as the leucocytic index and the sedimentation rate. In this table we find a correlation between the stage of the disease and the judgment as to whether the outlook for a patient is good or poor. In the former group there is a greater number of stage-II or moderately advanced cases, while in the latter the majority are classified as far advanced. However, six months after the operation no definite correlation is obtained as to tubercle bacilli in the sputum

TABLE 4

Clinical prognosis correlated with various factors in 47 cases of thoracoplasty

CLINICAL PROGNOSIS	ALL CASES	STAGE OF DISEASE		TUBERCLE BACILLI IN THE SPUTUM				UNIMPROVED SIX MONTHS AFTER OPERATION				DIED POST-OPERATIVELY	
		II	III	Before operation		Six months after operation		Haematologically		Clinically			
					per cent		*per cent*		*per cent*		*per cent*		*per cent*
Total.....	47	28	19	43	91.5	24	51	13	27.6	11	23.4	1	2.1
Good	15	12	3	14	93.3	9	60	5	33.3	6	40		
Fair	21	13	8	18	85.7	10	47.6	6	28.6	2	9.5		
Guarded	6	2	4	6	100	3	50	2	33.3	2	33.3	1	16.6
Poor	5	1	4	5	100	2	40	0	0	1	20		

or those haematologically and clinically unimproved. Rather, there is a tendency to have a smaller percentage of unimproved cases in the group clinically judged to have a poor outlook. As the clinical judgment attempts to predict the ultimate outcome of the cases too much emphasis cannot be put on this lack of correlation six months after operation. The fact remains that the leucocytic index and the sedimentation rate, both before and after operation, show a better correlation with the actual results obtained clinically in the same six-months period. Those patients with marked polymorphonuclear leucocytosis, as indicated by a high leucocytic index, with a shift to the left of the neutrophiles and a rapid sedimentation rate before operation, are actually those who constitute, in many instances, the poor risks.

Although a fairly good correlation was obtained between the leucocytic index and the sedimentation rate before operation and the clinical course of the patient after operation, it is evident that many with an unfavorable leucocytic index and high sedimentation rates show post-

TABLE 5

Serial blood examinations in 4 selected patients before and after thoracoplasty

The normal average for the band forms or the *Stabkernige* neutrophiles is 4 per cent. The upper limit of normal of the sedimentation rate is 0.4 mm. per minute.

Case number	1			2			3			4		
Age	19			53			21			40		
Stage of disease	II			II			III			III		
Tubercle bacilli in sputum	Negative			Positive			Positive			Positive		
Prognosis	Good			Good			Poor			Poor		
MONTHS	Leucocytic index	Sedimentation rate mm./min.	Band forms	Leucocytic index	Sedimentation rate mm./min.	Band forms	Leucocytic index	Sedimentation rate mm./min.	Band forms	Leucocytic index	Sedimentation rate mm./min.	Band forms
Before operation			*per cent*			*per cent*			*per cent*			*per cent*
12	33	.52										
9										17	2.05	12.0
6	31	.83	3.5				36	1.15	7.0	27	1.95	1.0
4		Home		24	.30	9.5	28	1.18	2.5	23	1.15	4.5
2	51	.86	1.0	21	1.20	19.0	16	.88	3.0	31	1.55	4.5
1	59	.89	1.5				8	.98	1.5	36	1.40	2.0
After operation	Operation			Operation			Operation			Operation		
1	52	.95	3.5	25	1.50	5.0	6	1.05	1.5	14	.70	7.5
2	14	.60	0.5	25	1.00	10.0	22	.50	19.0	0	.92	4.0
4	31	1.15	4.0	30	1.50	7.5	11	.50	1.0	0	.98	3.0
6	53	1.65	17.0	30	1.57	5.0	19	.50	2.0	4	.58	4.0
Tubercle bacilli in sputum	Positive			Positive			Negative			Negative		
Clinically	Unimproved			Unimproved			Improved			Improved		

operative improvement. The data so far considered were taken at fixed times, namely, before operation and six months later. As was pointed out above, in many cases there is a constant shift from one group to another over a period of time. In table 5 is demonstrated the trend of activity of the pathological process, as reflected in the blood, by

the serial examination of 4 selected patients. They illustrate how serial blood examinations may be practically useful in the selection of the patient for thoracoplasty, and the reason why certain cases when classified at a particular time, although in an unfavorable group haematologically, may be relatively good risks. Some of the salient points about these patients are recorded in table 5.

Cases

1: A young girl with a history of three years' duration. The first symptom was haemoptysis, when X-ray showed involvement of the right apex. A bed-patient at home for five months, she entered the sanatorium, where she remained for twenty-seven months, fourteen of them as a bed-patient. On admission, she had a cavity at the right apex, and artificial pneumothorax was attempted unsuccessfully. Right phrenicectomy was performed two months after admission. The patient improved clinically and roentgenologically, and the sputum, positive for tubercle bacilli, became negative and remained so for two years prior to operation. She was discharged to her home, quiescent, to return later for the consideration of thoracoplasty as a *prophylatic measure*, and to ensure, as far as possible, against future reactivation. She was readmitted four months later, and was accepted, somewhat under protest, for thoracoplasty, which was felt not to be a necessary therapeutic procedure. She was in a fine general condition, and the prognosis was considered good. An upper-stage thoracoplasty was performed, and immediate convalescence seemed uneventful. Shortly after operation, she began to raise sporadically large quantities of sputum which at times was found positive for tubercle bacilli. Seven months after operation there was X-ray evidence of extension to the right base.

For one year before operation, the leucocytic index in case 1 was high and in the group classified as unfavorable while the sedimentation rate was but slightly increased (see table 5). Up to the time of operation, even under sanatorium care, the sedimentation rate increased slowly but progressively, and the leucocytic index on readmission had reached higher levels. After the operation, there seemed to be both clinical and haematological improvement temporarily; then the haematological aspect began to change rapidly, with a sudden increase in both the sedimentation rate and the leucocytic index. Clinically, the patient was well enough to become ambulatory four months after the operation. At the time of the last determination recorded in the table there was marked reactivation of the disease, both clinically and roentgenolog-

ically. X-ray, taken 10 days prior to the last blood examination, however, was clear.

This case was chosen to illustrate that pathological activity was present all the time, gradually increasing even with sanatorium care. At the time of the operation we were dealing with an active process, and actually the operation was performed on a slowly "falling market," an expression borrowed from the surgeon, Dr. Edward D. Churchill, who has operated on all our cases.

The next case showed essentially the same feature as the previous one haematologically, but its evolution was much more rapid.

2: A male of 53 years, with a history of three years' duration and an insidious onset. He had spent the entire time in various sanatoria until transfer to Rutland. During the year before admission he had had attacks of indigestion and abdominal distress, with some loss of weight. On admission he was accepted as an excellent case for thoracoplasty, a chronic moderately advanced case in good general condition. There was a cavity at the right apex and the sputum was positive for tubercle bacilli. The only contraindication to operation was the patient's age. Nothing strikingly abnormal was found in the blood on admission except a slight neutrophilic shift to the left. Two months later, however, there occurred a rapid increase in the sedimentation rate and a marked neutrophilic shift to the left, while the leucocytic index remained the same. Clinically and roentgenologically no changes were noted in the patient's condition. On his return to the sanatorium after an upper-stage thoracoplasty, X-ray showed extension of the pathological process throughout the right lung. Since the operation, now sixteen months ago, the patient has not improved. He has considerable cough and 2 ounces of sputum positive for tubercle bacilli on every examination, he is losing weight, and his general condition is poor. The unfavorable trend of the leucocytic index, but especially the sedimentation rate, is illustrated in the table.

The evolution of the pathological process in this case illustrates how essential it is to get all the information available from the blood examination. Before the operation the reactivation of the pathological process was well advanced and the neutrophilic shift to the left and rapid increase in sedimentation rate were the only evidences available to indicate increased activity in an essentially chronic process.

In contrast to these cases are the two following who had clinically much less favorable outlook.

3: A male, of 21 years, with history of haemoptyses six and three months before admission. All other symptoms were denied. Sanatorium care was

advised after the second haemorrhage. On admission, X-ray showed fine mottling throughout the right lung with a cavity at the apex. Artificial pneumothorax was attempted, but unsuccessfully, and the prognosis was therefore considered poor. Two months after admission the right phrenic nerve was crushed. The sputum decreased in amount but remained positive for tubercle bacilli, and X-ray showed an increased diameter of the right apical cavity. An upper-stage thoracoplasty was performed and, after operation, the patient did exceptionally well, clinically, roentgenologically and haematologically, except for a slight flare-up of temperature with leucocytosis one month after his return to the sanatorium. Before the operation, haematologically, this patient was constantly improving; and, from being in an unfavorable group on admission, he had shifted into the favorable group before operation.

The next patient illustrates essentially the same features as in case 3 with some exception.

4: A male of 40 years, with a four months' history. The onset was acute, febrile, with cough, expectoration, pleurisy, and loss of 20 lbs. in 5 months. On admission, the general condition was poor, and the patient was classified as far-advanced, with poor prognosis. There was involvement throughout the left lung, with apical cavities, and also involvement of the right apex. Artificial pneumothorax on the left was unsuccessful, and phrenicectomy and scaleniotomy were performed three months after admission. The patient improved clinically, and thoracoplasty was considered but was deferred because of the poor general condition. A two-stage thoracoplasty was performed nine months after admission. After the operation the patient felt well and improved clinically, and he has been made ambulatory. On admission, he had a leucocytic index of 17 (50 per cent neutrophiles and 30 per cent lymphocytes), which gradually increased until, just before operation, he passed into the very unfavorable group (see table 5). This latter index corresponds to a practically normal differential count (except for an increase in the monocytes), which, according to Medlar (5), is abnormal or unfavorable in the tuberculosis patient. However, the sedimentation rate decreased and the neutrophilic shift to the left disappeared, again showing that, to evaluate the pathological process in its proper perspective, one ought not depend upon one factor alone, such as the leucocytic index, which in this case indicated that the patient was getting worse.

In our previous tables this patient belonged in the very unfavorable group preoperatively with regard to both the leucocytic index and the sedimentation rate, while actually, when the trend of the various haematological factors is examined, it showed improvement in general. Since

the operation the leucocytic index has been most favorable, the percentage of lymphocytes exceeding that of the neutrophiles. The sedimentation rate is also showing further decrease, but is still considerably above normal. Examining the trend of this patient's progress, as reflected in the blood, confirmatory evidence is obtained that the chances are good for obtaining benefit from the operation in spite of the clinically poor outlook.

The same general principles as to the relation between pathological activity, as reflected in the blood, and resistance of the patient seem to apply to the small number of cases in this series with empyema. Of the 7 cases that have had thoracoplasty, four had a high leucocytic index and belonged in the very unfavorable group, while three had a leucocytic index between 26 and 35 and thus belonged in the unfavorable group. All but one had a sedimentation rate above 1.0 mm. per minute, and four had a neutrophilic shift to the left. Of the 7 cases, one died postoperatively, and one has failed continuously and is now moribund, eight months after operation; two are doing well, both clinically and haemotologically; while three have draining sinuses, show some improvement clinically, but not haematologically, and are waiting for future surgery.

In the light of the above studies how can the query with regard to the value of blood studies in the selection of cases for thoracoplasty be answered?

In this comparatively small series of 47 cases the correlation of pathological activity (as revealed by the leucocytic index, the sedimentation rate and the neutrophilic shift to the left) and the clinical status of the patient before and six months after operation have given us a few concepts, which, when adhered to, might prevent a certain number of immediate failures of thoracoplastic collapse therapy. No one can be optimistic enough to believe that all failures can be eliminated, because of the inherent nature of the disease and because any major operation involves some risk. In retrospect, however, some of the poor results might have been prevented if the significance of the trend of the pathological process, as revealed by blood studies, had been fully realized. Thus, from the above analysis it is seen that the majority of the cases that have not done well after operation belonged to a group which one may designate as haematologically or pathologically unfavorable, with regard to either the leucocytic index, or the sedimentation rate or the

neutrophilic shift to the left, singly or combined. The real significance of the patient's status, however, was revealed only by serial examinations. Patients who under sanatorium regimen showed an increase of activity in the blood shortly before the operation did not withstand thoracoplasty successfully and did not show improvement during the six months' period here considered. Also, patients with marked but stable pathological activity showed a larger percentage of cases in which the sputum remained positive for tubercle bacilli after the operation. However, patients with considerable activity pathologically, but with the trend in the blood constantly improving, seemed to have a considerable chance of deriving benefit from the operation. Also, it is of special importance to have blood studies of the patient who appears clinically well and in whom it is difficult to evaluate the proper status of activity. In all the patients the indications for thoracoplasty may be present and blood studies may be of little value in selection from that point of view. They may, however, be of great value and perhaps indispensable to the clinician and surgeon for selecting the *time* of the operation, since a drastic procedure like thoracoplasty, with its drain on the patient's strength, if done at a moment when pathological activity is increasing may tip the scale irrevocably in the wrong direction.

The question is often asked as to what index or examination of the blood gives the best information about the pathological status of the tuberculous process.

One must always bear in mind, in evaluating the abnormalities in the blood in pulmonary tuberculosis, that the changes occurring are not specific for the disease but represent a reaction to injury. They differ from other reactions to injury mainly by their slow evolution and chronicity. Realizing this limitation, it is also probable that the mechanism by which changes occur in the leucocytes and differential counts and sedimentation rate are different, and that the two examinations supplement each other. A change in the leucocytes occurs, apparently, before the sedimentation rate is significantly altered. The leucocytic count is influenced, not only by the disease process, but also by the patient's ability to react to injury. The sedimentation rate seemingly expresses a condition or state of the body, and we have evidence to make us believe that the sedimentation rate in tuberculosis will persist long after the leucocytic reaction, and that it indicates much more delicately the healing of diseased tissue than do the leucocytes. And, in the markedly chronic stage of the disease, when low polymorphonuclear

counts are often found, the neutrophilic shift to the left is of singular importance in showing the degree of activity or reactivation of the tuberculous process. Consequently all these examinations are essential, as has been shown above in many cases. In addition, the red blood cells or haematocrits and haemoglobin give much valuable information. That it is practically possible to secure these data has been shown at the Rutland State Sanatorium, where serial examinations are done on every patient admitted.

SUMMARY

Blood studies, including the corrected sedimentation rate and leucocytic counts, have been analyzed and correlated to various factors in 47 cases of pulmonary tuberculosis, prior to thoracoplasty and six months after the operation.

The leucocytic counts are expressed in terms of the leucocytic index of Medlar in order to evaluate this index from the clinical point of view.

CONCLUSIONS

1. Patients with a favorable leucocytic index and with a normal or practically normal sedimentation rate before a thoracoplasty are likely to respond well to the operation.

2. Patients with marked activity of the disease process, as revealed by the leucocytic index and the sedimentation rate, likewise respond well if the trend of the blood, as revealed by serial examinations, indicates progressive improvement before the operation.

3. Patients, who shortly before the operation show an increase in the sedimentation rate, the leucocytic index and a neutrophilic shift to the left on serial examinations, do not derive the expected benefit from the operation and some are made definitely worse.

4. More reliable information is obtained by evaluating all factors combined than by the consideration of a single factor alone.

5. Blood studies constitute a valuable addition to the standardized clinical and laboratory procedures now in use in pulmonary tuberculosis for the selection of the appropriate time for thoracoplastic operation.

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THE THORACOTOME AND ACCESSORY INSTRUMENTS FOR THE SEVERANCE OF INTRAPLEURAL ADHESIONS THROUGH A SINGLE CANNULA

J. W. CUTLER[1]

Since the publication of the first description of the Cutler operating forceps thoracoscope (1) (2) and other instruments for the intrapleural severance of adhesions through a single cannula, I have had opportunity to modify materially some of these instruments and add several new ones.

Figure 1 illustrates the present thoracotome. This instrument was originally designed for short adhesions, of the type that is usually broad and vascular with insufficient space between lung and chest-wall to permit entrance of the jaws of the forceps thoracoscope. It was also designed for enucleation of adhesions situated at difficult and otherwise inaccessible angles (figures 1, 2 and 3). To use the forceps thoracoscope under such circumstances would result in disaster through cauterization of lung substance.

The electrode consists of a narrow wire loop, hinged to permit angulation and securely held in an insulated bushing at the distal end to give stability. It is arched forward to bring the bend of the electrode within the field of vision when the instrument is perfectly straight. The posterior limb of the electrode is insulated to prevent accidental cutting of tissue, and at the junction of the posterior limb and loop there is a small bead which serves as a sight to facilitate vision.

After the instrument has passed through the cannula into the pleural cavity and before the electrode has been applied to the adhesion, it should be angulated by manipulating the handle near the eye-piece until the tip of the electrode occupies the centre of the visual field. Once the proper position of the electrode is determined, no further manipulation of the instrument is necessary. The angulating feature is essential; otherwise the electrode would be too large to pass through the small cannula employed. The hinged bushing is made short in

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Fig. 1

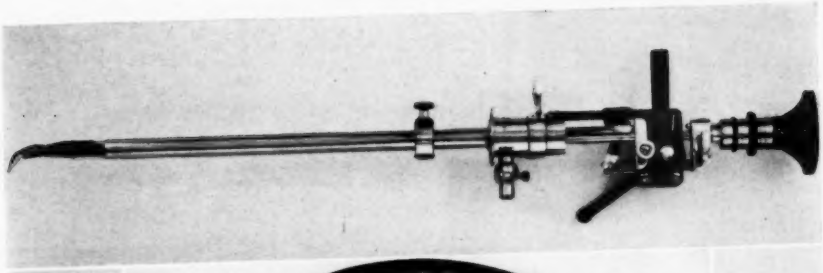

Fig. 2

Fig. 3

order to bring the tip of the electrode as near to the telescopic lens as physical limitations would permit.

The electrode can be applied to any given point within the pleural cavity with exacting accuracy, and under the full vision and control of the operator, even though the tip of the electrode is buried within the adhesion during the course of the operation. The characteristic manner in which the electrode is mounted in the bushing gives it the desired stability.

It will be noticed that the actual severance of the adhesion is carried out with a small loop of wire rather than with a point. My experience with pointed electrodes has been unsatisfactory, as bleeding was too frequent a complication. This is rendered much less likely with the present construction of the electrode, as the loop contacts a larger surface of the adhesion and coagulates it thoroughly before actual severance begins. On the other hand, the electrode is sufficiently delicate to permit careful dissection in close and difficult quarters.

The thoracotome follows in construction the same general principles described for the Cutler forceps thoracoscope in that coagulation and cutting is carried out as a continuous process by means of a low current acting through a single wire electrode of moderate thickness. The source of current is the vacuum-tube type of high frequency machine. The manufacturers hold that the spark-gap machine is apt to destroy the working part and electrode, melt the lamp and lens, and bake the tissue tight to the electrode.

Figure 4 illustrates the modification of the curved, coagulating, cutting electrode described previously. The blades have been thickened to assure thorough coagulation before severance of the adhesion begins. With proper technique bleeding is practically made impossible, a complication which could not always be avoided with the older type electrode. The insulated supports for the electrode have also been materially strengthened to give the electrodes greater stability during the act of cutting.

Fig. 1. Assembled thoracotome

Fig. 2. The severance of a short adhesion with the thoracotome. The electrode coagulates and cuts along the line of cleavage which can usually be made out near the chest-wall. Many extensive adhesions considered inoperable can be managed in this way.

Fig. 3. Enucleation of lung attachment with the thoracotome. No attempt is made to enucleate the entire attachment at one operation. Properly spaced pneumothorax refills will stretch the remainder, and either make further operation unnecessary or, when indicated, a simple procedure. Enucleation materially widens the usefulness of pneumonolysis.

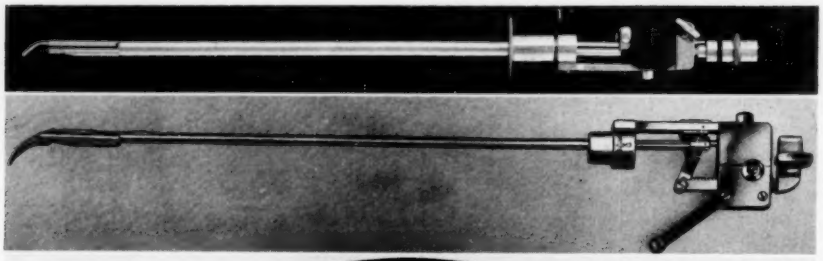

Fig. 4

Fig. 5

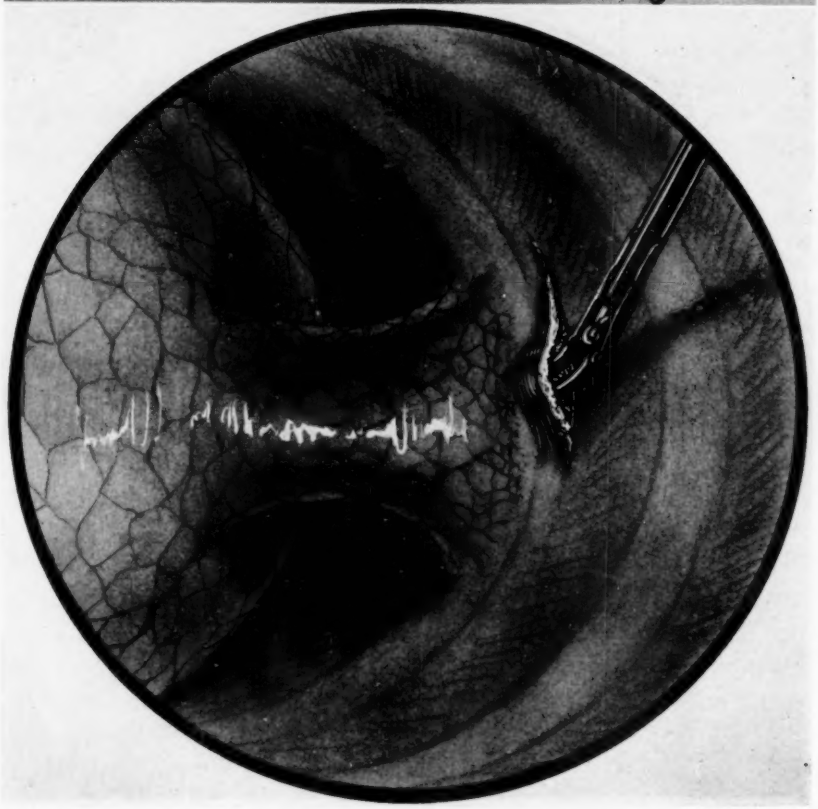

Fig. 6

Fig. 4. Improved coagulating, cutting, curved electrode assembled in utility carrier and cannula

Fig. 5. The blunt dissector

Fig. 6. The blunt dissector is used to undermine the base of the attached lung, once a point of entrance has been made with the thoracotome along the parietal pleura. It carries no electrode and acts as a companion instrument in the procedure of enucleation.

Fig. 7

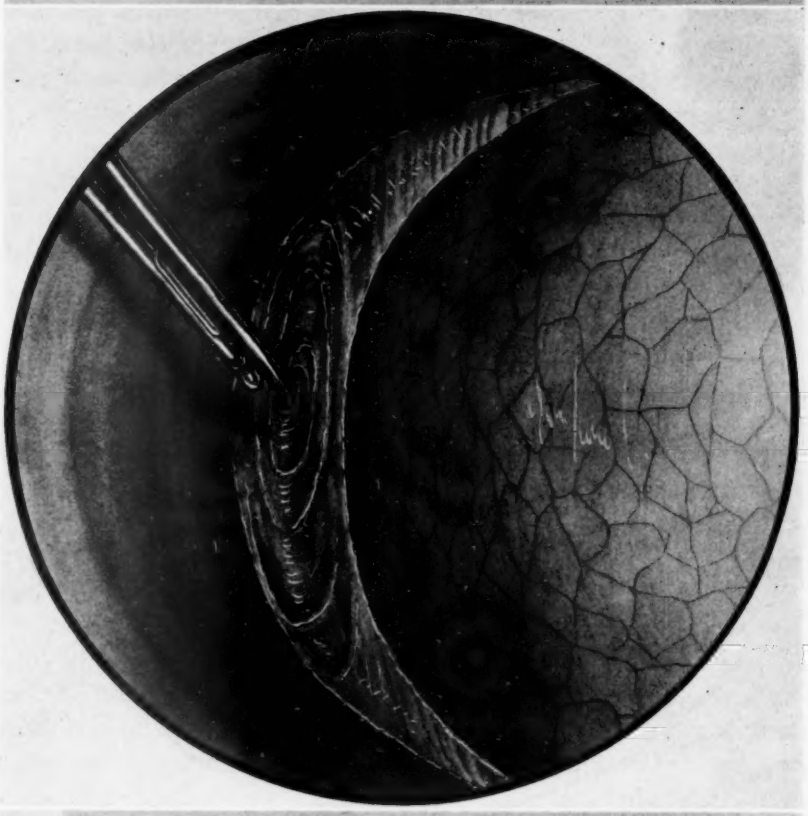

Fig. 8

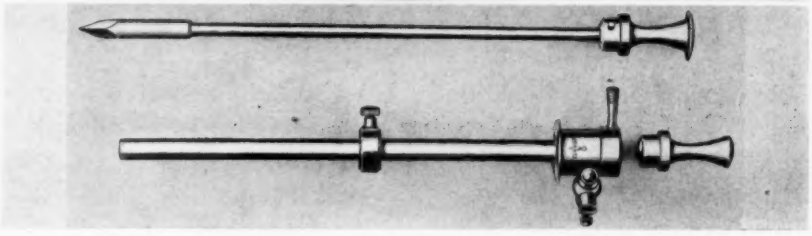

Fig. 9

Fig. 7. Thoracoscopic aspirator

Fig. 8. The thoracoscopic aspirator is a useful instrument and should always be available. It is easy to control and vision is excellent.

Fig. 9. Improved trocar and cannula

These electrodes fit securely into the utility carrier and are designed for that small number of troublesome adhesions which cannot always be handled efficiently with the thoracotome, as under certain operating conditions the end of the electrode of the thoracotome is a little too distant from the telescopic lens for perfect work. The curved electrodes, however, do not take the place of the thoracotome, as they lack the angulating feature and other advantages which become apparent when the thoracotome is used.

As useful as these instruments are, they are not intended to take the place of the forceps thoracoscope, as the latter has advantages peculiar to itself and is indispensable in the author's single cannula technique. The forceps thoracoscope, thoracotome, and curved cutting electrode are companion instruments and were designed to complement and supplement each other. All should be available.

The blunt dissector (figure 5) is a new development. It carries no electrode, and in a sense serves as a mechanical finger. It is intended primarily to peel off apical cap adhesions and for enucleation, once a start has been made with the thoracotome (figure 6). It can also be used to inspect and "palpate" questionable adhesions before cutting. I shall describe its use in greater detail in the near future.

Occasionally I have felt the need of an aspirator to remove blood that might have accumulated within the pleural cavity during operation or fluid that might have gravitated to the operating field during the course of the operation. This can be accomplished with the author's aspirator (figures 7 and 8), to which one can attach a syringe or pump. The barrel of the aspirator is also designed to serve as a carrier for a thoracoscopic needle or haemostatic forceps, as the case may be. This simplifies the use of these accessories and reduces the number of instruments required to a minimum.

The original trocar and cannula has also been improved in several respects (figure 9). The knob of the trocar has been broadened and shaped to fit the palm of the hand. Pins have been added which lock the trocar securely in the cannula making it impossible for the trocar to become loose during the procedure of passing the trocar and cannula through the chest wall. The specially designed plug makes it possible to close the opening of the cannula when no instruments are in place and in that way prevent avoidable loss of air from the pleural cavity. The cannula also carries a two-way valve for attachment with the

pneumothorax apparatus when it is desired to inflate the pleural cavity with air during operation.

The development of the instruments illustrated has made it possible to widen the usefulness of the single cannula technique and to sever the more complicated types of adhesions and those "difficult to reach" with greater ease and safety than was possible heretofore.

I wish to acknowledge my indebtedness to Mr. F. C. Wappler and to Mr. M. R. Peck of the American Cystoscope Makers of New York for their coöperation in the development of these instruments.

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SPONTANEOUS HAEMOPNEUMOTHORAX

Report of a Six and One-Half Year Follow-Up of a Case[1]

A. T. MILHORAT

Spontaneous haemopneumothorax is a rare condition. In a recent report of a case, Frey (1) reviewed the literature and was able to collect only thirteen cases that had been reported. In none of these was the patient followed for a period longer than six months. Since it is of interest to know what the future fate of patients with this condition might be, the present report representing a six and one-half year follow-up on a patient is presented.

A brief abstract of the report of this case which the writer published in 1931 (2) is as follows:

The patient was a twenty-one year old Cuban male whose past history was irrelevant except for pleurisy without effusion eleven months previously. On May 2, 1929, he suddenly developed a steady pain in the left shoulder while riding comfortably in the subway. The pain later spread to the precordium and gradually extended to include the whole left chest. Twelve hours after the onset of symptoms, he developed a pain in the abdomen, with tenderness over McBurney's point and below the left costal margin. Because of the prominence of the abdominal signs the patient was referred to the Presbyterian Hospital, New York City, with the provisional diagnosis of acute appendicitis. After a careful physical examination, it was believed that the abdominal pain, rigidity and tenderness were secondary to the condition of the thorax. The left chest was markedly hyperresonant throughout except below the level of the 6th rib where there were flatness and egophony, and the spoken and whispered voice sounds were greatly diminished. A definite succussion splash could be heard. The trachea was deviated to the right, and the heart was displaced to the nipple line on the right side. Exploratory thoracentesis of the left chest yielded pure blood which was sterile on culture. Radiograph of the chest showed a large amount of fluid in the left chest with a very definite fluid line at the level of the 5th rib. At the top of this fluid the lung was collapsed and replaced by air. The heart shadow was displaced to the right and the right lung field was clear.

[1] From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York City.

Treatment was conservative, consisting of complete rest with liberal amounts of sedatives and seven small thoracenteses performed at weekly intervals. The patient improved slowly but steadily. Frequent radiographs of the chest and the physical signs demonstrated a gradual absorption of the air, and a progressive reëxpansion of the collapsed lung. At the time of the patient's discharge from the hospital, fourteen weeks after the onset of his illness, only a small amount of fluid still remained. The left chest showed some flattening and the intercostal spaces on that side were narrowed. No evidence of tuberculosis or of purpura could be found. Repeated sputum examinations showed no acid-fast organisms. The thoracentesis fluid was

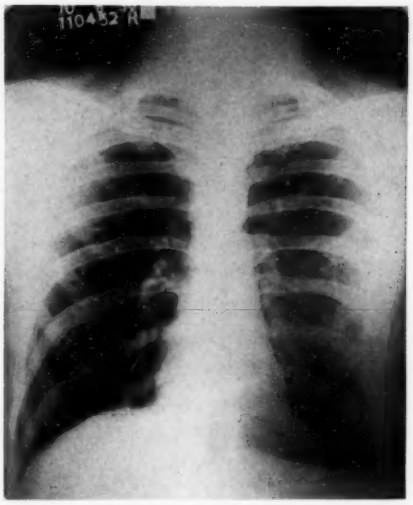

Fig. 1. Radiograph taken October, 1935, six and one-half years after occurrence of spontaneous haemopneumothorax

persistently sterile on culture and produced no tuberculosis when injected into a guinea pig. No shadows suggestive of tuberculosis could be seen in the radiograph of the right lung or of the reëxpanded left lung. The bleeding time, clotting time and platelet count of the blood were normal.

A radiograph of the chest taken four months later showed that the fluid was almost completely absorbed. The pleura in the lateral area on the left side was thickened, but the apical areas and the lung parenchyma were clear. There was moderate narrowing of the intercostal spaces on the left side. Nine months after his accident the patient reported that he had gained weight, had returned to work, and was free from all symptoms in any way suggestive of his former illness.

In October, 1935, the opportunity of examining the patient again was presented. He had returned to Cuba shortly following his illness in 1929 and had remained in his native country up to the time of this recent visit here. For the past six years the patient had worked steadily and had been entirely free from symptoms. There was no history of weakness, cough, haemoptysis or night-sweats. His weight had increased steadily from 160 lbs. in 1929 to 190 lbs. in 1935. In 1931 he had a tonsillectomy. Since then he had had no colds although previous to this operation he had frequent colds all the year round.

On October 2, 1935, the patient entered the Out-Patient Department of the New York Hospital. His appearance was that of a well-nourished young male in good health. The left thorax was markedly retracted, but the respiratory excursion appeared normal. There was moderate dulness and diminished breath- and spoken voice-sounds over the left lung. These signs were more marked below the axilla. No friction rub was heard. The rest of the physical examination revealed no abnormal findings.

A radiograph of the chest showed moderate flattening of the diaphragm on the left side. The costophrenic angle on the right side was clear, but on the left it was shallow. The right lung field was essentially negative. On the left side there was evidence of considerable thickening of the pleura in the lower lateral lung field, with an irregular distribution of calcium in the lateral portion of this area, and moderate haziness in the medial portion of the same area. The lung markings did not appear unusual. The pleura at the apex was moderately thickened. The findings were consistent with an old pleural involvement with some fixation of the diaphragm, thickening of the pleura and evidence of calcification of the pleura. There was no evidence of recent parenchymal involvement.

A comparison with the radiograph taken nine months after the onset of the illness shows that the following changes had occurred during the six year period: (1) calcification of the pleura in the areas discussed above, and (2) thickening of the pleura at the left apex. The latter finding, which is probably the result of an old apical tuberculous lesion, suggests that the haemopneumothorax might have been caused by a tuberculous process. However, no further evidence of this can be demonstrated. The clinical course after the occurrence of the haemopneumothorax was one of progressive improvement. For the past six years the patient has enjoyed excellent health with freedom from all symptoms suggestive of pulmonary disease.

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TUBERCULOUS LARYNGITIS

The Basis of Its Symptoms and Treatment

B. T. McMAHON[1]

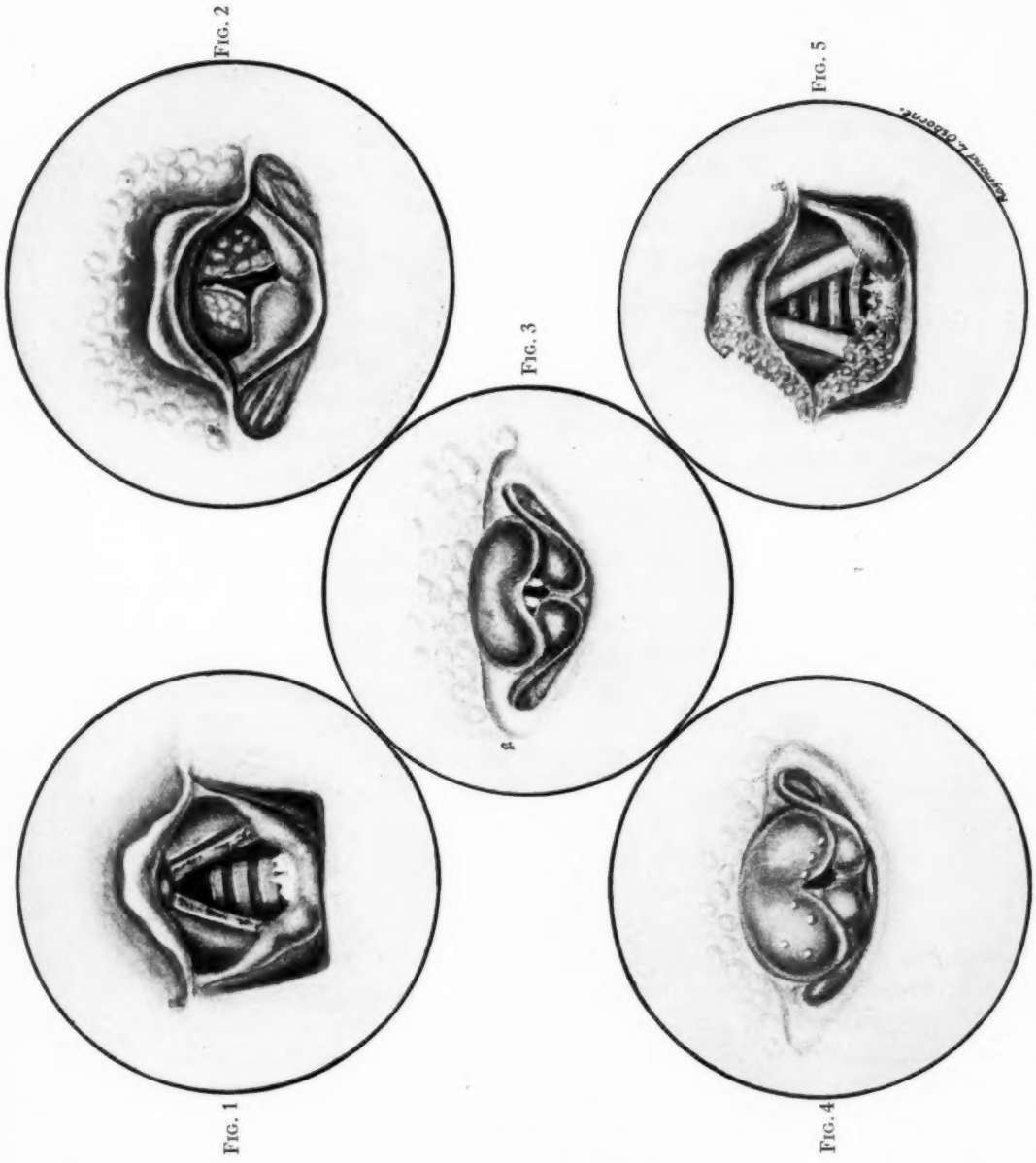
The object of this paper is to correlate modern conceptions of the pathogenesis and pathology of tuberculous laryngitis with symptoms and treatment.

The reported incidence of tuberculosis of the larynx varies considerably. In an institution taking all types of cases, such as Loomis Sanatorium, the incidence is about 15 per cent, men and women being equally affected. It is very rare in incipient and relatively common in far-advanced pulmonary tuberculosis.

PATHOGENESIS

For all practical purposes tuberculosis of the larynx may be considered as secondary to pulmonary tuberculosis. The larynx becomes involved in two ways: (1) from surface contamination by infectious exudate discharged from the lungs, that is, by intracanalicular spread, and (2) through the blood-stream. When resulting from intracanalicular spread, there is a predilection for the intrinsic structures, such as the true and false vocal cords and the posterior commissure, and the lesion is usually asymmetrical. Fränkel has shown the tubercle bacillus to be capable of penetrating intact mucous membrane. Other portals of entry for the bacillus are the excretory ducts of the mucous glands of the larynx and the epithelial defects resulting from coughing and "hacking." In acute haematogenous miliary tuberculosis the larynx may be involved. In the course of chronic pulmonary tuberculosis spread of the disease within the lungs is usually the result of infection conveyed to different parts by way of the bronchial tree. Not only in acute generalized miliary tuberculosis, but also in subacute or protracted haematogenous dissemination, it is now recognized that the lungs may participate with lesions of varying character. Similar types of lesion are encountered in the larynx. The site of election is the extrinsic structures and a symmetrical involvement of the epiglottis, arytenoepiglottic folds and

[1] Loomis Sanatorium, Loomis, New York.



FIGS. 1 TO 5
For description see text

the arytenoids is characteristic (figure 3). There is little intrinsic involvement. Because of its symmetry and absence of ulceration it is difficult to explain the pathogenesis of such a lesion on the basis of a surface infection. The pulmonary tuberculosis accompanying this type of lesion consists of small focal deposits symmetrically distributed in the upper two-thirds of both lungs. Figures 1, 2 and 5 show typical lesions resulting from infection by surface contamination. Mixed types of haematogenous and bronchogenic seeding are met with in the lungs and larynx. In figure 4 is shown an example of this. There was first disease of the left vocal cord and posterior commissure complicating a lung lesion with cavity. Later a haematogenous spread involved both lungs, the epiglottis, its folds, and the arytenoids.

PATHOLOGY

Manasse's (1) excellent handbook on the pathology of tuberculosis of the upper respiratory tract is lucid and readily applicable clinically. He described four main changes in the larynx. There is, first, *infiltration* which may be local or general and consists of round cell infiltration and tubercle formation in the submucous coats. It may be accompanied by a fine or coarse meshed oedema. As an example, figure 2 shows a localized infiltration of the right arytenoid. In figures 3 and 4 are shown more advanced lesions with massive infiltration with oedema involving the epiglottis, its folds, and the arytenoids. There is a coalescence of tubercles and oedema. The terminal nerves are inflamed and there is proliferation of the nerve endings.

The second stage is *ulceration*, which is a sequel of infiltration. It begins as an actual intrusion of the as yet unbroken tuberculous granulation tissue in the submucous layers into the covering epithelium, which it apparently destroys by pressure necrosis. Manasse effectively disproves the commonly held view that ulceration is the result of the breaking down of tubercles, although he admits that in occasional instances ulceration may start in this way. In figure 2 are shown ulceration and destruction of the true cords and in figure 1 granulations arising from ulceration of the posterior commissure. The third stage is *perichondritis*, most frequently involving the arytenoid cartilages, the epiglottis, tracheal rings, and occasionally the thyroid cartilage. The actual inflammation of the perichondrium is not demonstrable but its presence is indicated by symptoms. It is generally present in the lesions of the types illustrated in figures 3 and 4, and probably also in the right aryte-

For description see text

noid as shown in figure 2. Perichondritis results from penetrating funnel-shaped ulcers with a wide inlet at the surface and a pointed extension into the depth. The funnel is filled with fine, granular, caseous masses and pus. Its walls consist of granulation tissue, the surface of which shows abundant necrosis. Perichondritis may result in liquefaction or complete necrosis of the cartilage. The final change described by Manasse consists of *tuberculomata and pachydermic thickenings*. Clinically such tumors are rare.

Since 1922, observation of a number of patients, suffering from tuberculous laryngitis and treated at the Loomis Sanatorium, has demonstrated a definite correlation between the location and stage of the pathological process and the resulting objective and subjective symptomatology. The symptoms of tuberculosis of the larynx may be divided into three main groups. First, paraesthesias, the commonest symptom of which is a tickling sensation in the larynx. This results from lesions of the posterior commissure. In the movements of adduction and abduction the mucous membrane is irritated by the deposits in the posterior fold (figure 1). In many cases the hard verrucous lesions in this area are detected only on routine laryngoscopy. The hard surface indents rather than irritates the mucous membrane, and is hence less provocative of tickling sensations than are the soft granulations (figure 1). The second group of symptoms consists of disturbances of the voice, varying from slight huskiness to marked hoarseness, or even complete aphonia. The chief cause of such symptoms is involvement of the true cords or interference with their movements. In figure 2 is shown ulceration and destruction of the true cords. The chief symptom of such lesions is marked hoarseness. The infiltration of the ventricular bands interferes with adduction and abduction of the vocal cords and further accentuates the hoarseness. The slight inflammation and loss of tone of the true cords (figure 1) cause mild hoarseness and a tendency to easy fatigability. These symptoms are aggravated by prolonged use of the voice. The third main group of symptoms is interference with the act of swallowing; most commonly, pain on swallowing. Figures 3 and 4 illustrate classical examples of these. In the act of swallowing, the contraction of the arytenoepiglottic folds produces pressure on the inflamed perichondrium of the arytenoids and epiglottis, and also irritation of the proliferated nerve endings and inflamed nerves. This gives rise to acute pain, usually referred to the ears. This pain is usually greater in swallowing fluids than in swallowing semisolids or solids. In

the swallowing of fluids the degree of contraction of the arytenoepiglottic folds is greater because of the need of more rigid closure of the epiglottis to prevent fluids getting into the air-passages; hence there is greater pressure on the inflamed perichondrium and nerve endings. These three main groups of symptoms are so characteristic that, from a careful history, it is usually possible to infer the type and location of the laryngeal lesion. If a tickling sensation is the chief complaint, involvement of the posterior commissure will be found. If interference with the voice is the outstanding symptom, involvement of the cords or interference with their function will be demonstrable. Pain or difficulty in swallowing indicates an extrinsic lesion with arytenoid and/or epiglottic perichondritis. A combination of symptoms points to a more widespread lesion. In advanced tuberculosis of the larynx, dryness of the throat is usually present in lesions such as illustrated in figures 3 and 4. In this type of case the mucous glands of the larynx secrete profusely to relieve thirst; but, to avoid the extreme pain provoked by swallowing mucus and saliva, the secretions are expectorated rather than swallowed. This loss, together with a reduced intake of liquids, increases the local dryness and contributes to dehydration of the tissues generally.

OBJECTIVE SYMPTOMS

Tuberculosis of the larynx resulting from surface infection tends to be unilateral and on the side of greater lung involvement. This circumstance is largely fortuitous, but may be explained in part by the fact that the patient tends to lie on the more affected side. The posterior commissure and vocal angle are the sites of greatest incidence, probably because of their dependent position and less efficient drainage. Haematogenous tuberculous laryngitis selects the extrinsic structures and is symmetrically distributed. The granulations produced by tuberculosis, as distinct from those of syphilis, are soft and furrowed, a point that Casselberry (2) considers of great clinical significance. Pea-shaped arytenoids are characteristic of tuberculosis. The larynx may heal while the lung lesion progresses, but if the larynx gets worse the disease in the lungs is almost invariably progressive. It is extremely rare for a patient whose larynx is not involved at the time of admission to develop tuberculosis subsequently in this region during sanatorium residence. At Loomis Sanatorium its development under such circumstances has usually been of grave prognosis.

DIAGNOSIS

In all patients with pulmonary tuberculosis the upper respiratory tract should be examined, as some 20 per cent of the cases with laryngeal involvement do not have subjective symptoms. In the differential diagnosis, conditions to be considered are catarrh, syphilis, trauma, epithelioma, pachydermia and malformation.

TREATMENT

As in tuberculosis elsewhere, the most important treatment of the larynx is rest. Any procedure which cuts down cough and expectoration will help the laryngeal condition. In this respect effective artificial collapse of the cavity-bearing lung produces the best results. Specifically, rest to the larynx is obtained by infrequent use of the voice, or silence. The commonest measure prescribed is "whispers;" but, without definite instructions as to how to whisper, the patient is likely to do more harm than good by resorting to the "stage whisper," which is a greater strain on the larynx than use of the voice. Emphasis should be placed on the proper way to "whisper." This should be a labial and lingual act,—not vocal. The patient is instructed to whisper the word "lips," and it is then pointed out how this sound is made in the mouth and by the lips, thus resting the larynx. If the patient finds this too difficult to practise, it is better to permit speaking slowly in a low tone, and as infrequently as possible rather than resort to the hoarse (vocal) whisper. When the vocal cords are severely involved, silence should be imposed.

Heliotherapy stimulates healing in diffuse indolent lesions. Where a constant supply of sunshine is available local exposures by means of metallic reflectors is indicated. In the majority of sanatoria, because of lack of sunshine, artificial heliotherapy may be supplied by quartz applicators attached to water-cooled arcs or through cold quartz. Sprays for cleansing purposes give symptomatic relief, but rarely affect the lesion. Topical applications have very limited indications, because they do not get at the seat of the lesion in the submucous coats, and their action is not limited to the diseased area. The actual cautery, on the other hand, has none of these disadvantages. It actually gets at the seat of the trouble and practically amounts to a specific in the treatment of tuberculosis of the larynx.

With the lesion exemplified in figure 1 the treatment indicated is removal of the granulation on the posterior commissure by the cautery.

This will relieve the tickling sensation and the coughing produced by it. The resulting rest to the larynx will be sufficient to permit the true cords to heal and regain their tone. In the case shown in figure 2 silence is indicated. On the other hand, the type of lesion depicted in figure 3 has little involvement of the true cords or interference with the voice; and, consequently infrequent use of the voice and speaking slowly and in a low tone are preferable to silence. This type of lesion produces pain on swallowing, and the treatment of choice is deep punctures with the actual cautery. In mixed types of disease, when there is hoarseness and pain on swallowing (figure 4), voice-rest and relief of pain are indicated. The excruciating pain of perichondritis is one of the most distressing symptoms in the whole field of tuberculosis work and its relief is ever a problem. Palliative measures recommended are inhalations through a Le Duc tube of equal parts of anaesthesin and orthoform powders, cocaine sprays, and injection of the external branch of the superior laryngeal nerve as it penetrates the thyrohyoid membrane. This last procedure does not give prolonged or substantial relief of pain. Recently Grain (7) has reported excellent results from the use of ionization. I have found it definitely helpful. Savitt and Soboroff (3) and also Echols and Maxwell (4) describe an operation for crushing or section of the main trunk of the external branch of the superior laryngeal nerve. When pain is the chief symptom and is not controlled by palliative measures, crushing of the external branch of the superior laryngeal nerve on one or both sides is indicated. Lesions of the type shown in figures 3 and 4 respond to igni-puncture with the cautery. The current is so set that the needle-like platinum tip comes quickly to a white heat. The tip is placed cold at the point of puncture; the current is turned on; and the point is inserted into the diseased part until the resistance of healthy tissue is met; and, with the current still on, the point is withdrawn, leaving a charred deep puncture. Terry (5) claims that the use of high frequency current gives greater relief of pain than the galvanic cautery.

PROGNOSIS

The capacity for tuberculous laryngitis to heal is much greater than is generally assumed. The vocal cords may be so destroyed by tuberculosis that only vestiges are visible on laryngoscopy and there be almost complete loss of voice; and yet regeneration can be so complete that, on superficial examination, the newly formed cords would pass for

normal and the voice would sound resonant and clear to a stranger. It usually takes one to two years to bring about such a change. On close examination the newly formed cords are lacking in lustre and the free margins are slightly rounded. The type of lesion shown in figure 1 may heal so completely as to pass for normal. The majority of cases of the type depicted in figure 4 die in a few months, as the disease in the lungs is active and progressive and unsuitable for collapse therapy; but occasionally there is a brilliant result. Generally speaking, the prognosis depends on the laryngopulmonary lesion as a whole. Thomson's (6) findings of a laryngeal complication adding to the severity of the pulmonary prognosis, that is, that a moderately advanced pulmonary tuberculosis with a laryngeal complication has the prognosis of far-advanced pulmonary disease, are in agreement with the results at Loomis Sanatorium.

The most effective prophylaxis lies in making a consistently negative sputum the objective of treatment in laryngopulmonary tuberculosis.

For the excellent illustrations I am indebted to Mr. Raymond L. Osborne, a senior medical student at the College of Physicians and Surgeons, Columbia University, New York.

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NERVOUS DISORDERS ASSOCIATED WITH PULMONARY TUBERCULOSIS

KARL SCHÄFFLE[1]

This subject is presented from the viewpoint of one who is not trained in neuropsychiatry but who has had to learn some of the elementary features of that field, in order to make any reasonable approach to success in the treatment of tuberculosis. The title is so worded as to include conditions which have been present prior to infection as well as those which are usually listed among the complications of tuberculosis. Some of these conditions may have been predisposing to the latter disease or simply may have developed along with it as vitality has weakened and toxaemia increased. We all know that probably a majority of our tuberculous patients are of high-strung, restless or ambitious type; many of them have succumbed to the disease through exhaustion of their nervous energy. Others may have inherited poor powers of resistance, a condition which is expressed in their nervous constitution as well as their susceptibility to infection.

Let us consider first the milder disorders, which are usually described as functional, and proceed to the definitely organic conditions, remembering, however, that we may have combinations, and that it is often difficult to determine where the functional leaves off and the organic begins. Among the first and most common of all is neurasthenia, so called.

This term is applied to that well-known condition of unaccountable fatigue, both physical and mental, with increased sensitiveness to all sensory impressions and consequent preoccupation with them until normal effort is impaired and the slightest task is dreaded. Any chronic illness is likely to be accompanied or followed by "neurasthenia" sooner or later. In fact, its idiopathic existence has been doubted. Infections which persist for weeks, months or years, with their speeding up of metabolism by fever and impairment of function by toxaemia, may have profound effects upon the nervous system. In tuberculosis fatigue is usually one of the first symptoms, often antedating the pulmonary by

[1] The Wm. LeRoy Dunn Memorial Clinic, Asheville, North Carolina.

long periods of time. Moreover, we seldom see the stage of emaciation of muscles, poor circulation, defective digestion and faulty elimination without marked signs of nerve exhaustion. This is characterized by irritability, modification of reflexes, sympathetic phenomena (flushes, sweats, large pupils), tremors, tics and even involuntary twitchings of entire extremities. The specific symptoms of cough and dyspnoea, frequently accompanied by pain in the chest, are in themselves sufficiently distressing, particularly in disturbing the patient's rest, to wear down the nervous mechanism. Weir Mitchell's "rest-cure" was beneficial in the majority of his patients who were suffering from nervous weakness. I have often wondered, since hearing him describe it years ago, how many of them might have shown evidence of pulmonary disease if they had been examined by the X-ray in those days.

In addition to the disease aspect, we have a form of treatment or regimen, which is to the majority of persons an abnormal way of life, consisting of enforced rest in a confining and, at times, a depressing environment. Certain restless individuals find it very difficult to adapt themselves to it, leaving sanatoria before recovery is established, spending a few fretful weeks at home or at some other resort and returning in worse condition than they were before. This was observed, some years ago, in thousands of ex-service men, who, through political influence, obtained transfers from one government hospital to another in various parts of the country until the matter almost became a public scandal. Of persons who find difficulty in adapting themselves to the sanatorium regimen, there are at one extreme those who are rather robust, with active minds, who feel so well that such restriction seems to be "all foolishness," while at the other end are those who are so toxaemic that they are highly irritable and find fault with everything about them and with every measure which is taken in their behalf. Fortunate are those patients who have some symptom which is sufficiently impressive to make them comply with regulations, but not so alarming as to haunt them with fear. As in replying to new patients who ask about the extent of their involvement, the words of Mercutio may be used but without their sinister implication, " 'tis not so deep as a well, nor so wide as a church-door, but 'tis enough."

Following closely upon neurasthenia, is a disturbance which presents more spectacular features,—hysteria. After months of being waited upon by physicians and nurses and being the object of inquiry by visitors, some patients become highly egocentric and subject to the petty

jealousies of institutional life. Adults who have been in bed for some time are more or less influenced by such association and tend to revert to the traits of childhood and a sheltered existence. They feel hurt if they don't receive as many callers, flowers, books, packages of fruit or candy as those about them and are quick to take offense if teased, or to feel neglected if passed over too quickly or if some other patient is given more attention, even though it is obviously needed. This leads to insomnia and loss of appetite, with conscious or unconscious exhibitions of symptoms that will concentrate attention upon themselves. These may be simply an increase in their usual pulmonary symptoms or the development of digestive disorders, but they are likely to extend to any of a number of inexplicable and bizarre phenomena which we ordinarily regard as manifestations of hysteria. Of course, the typical hysteric has certain recognizable stigmata, including physical and mental signs of immaturity and, among the latter, chiefly heightened suggestibility. Such patients complain of the classical *bolus*, or lump in the throat, especially if laryngeal tuberculosis is feared; of greater weakness than appears to be warranted, particularly of some special part as the upper or lower extremities; or of intense headache, impairment of vision, dizziness, palpitation and burning sensations of a vague character in the abdomen or other parts of the body. They may suddenly display violent tantrums of temper or stage seizures indicative of epilepsy or mania. There may be a suggestive history in such cases, with accentuation of previous tendencies by disease and its treatment.

There are certain conditions which are evidently more than functional, but in which it is difficult, at times, to find a definite lesion as a cause. Prominent among these is migraine, which is now classed by some among the allergies. In this connection it is interesting to note that the usual description of its victims corresponds fairly closely to that of a certain type of "consumptive," frequently the subject of romantic literature,—highly intelligent, with finely chiselled features of classical cast, delicate pale skin of transparent waxy character with veins showing through, hair of fine texture and prominent eyes with dilated pupils,—the angelic type. Yet, may not several of these characteristics be but evidences of a highly functioning thyroid?

Another nervous affection recently listed among the allergies, and, like migraine, probably antedating the tuberculosis by many years, is epilepsy. Here, as in the preceding condition, there is likely to be a rather peculiar psychological picture with a tendency toward ego-

centricity and exaggeration with a lack of dependability and, possibly, even deceitfulness.

Facial and other tics, particularly involuntary muscular contractions in the limbs and abdomen, may be listed here and are sometimes quite troublesome, resulting in physical exhaustion if allowed to continue too long. Persistent hiccough may be a serious complication.

Among the neuralgias, those of the intercostal nerves are frequent and are naturally confusing with pleurisy. There are also facial neuralgias which are usually due to one or more of the common focal infections. Pain in the shoulder and neck, with limitation of motion, may be referred from pleural adhesions, especially diaphragmatic, which the X-ray will often disclose as "tentings."

As to endocrinology, it is a matter of common knowledge that tuberculosis is one of the most frequent causes of dysmenorrhoea or amenorrhoea. This may be temporary until vigor is restored as a result of definite improvement in the pulmonary condition; it may be partial, consisting of scant and irregular menstruation with long intervals between periods; or it may be permanent in a patient who fails to improve or whose age approaches that of the normal menopause. In any of these phases there is likely to be considerable nervous disturbance, as expressed by weakness, dizziness, tremor, palpitation, indigestion, insomnia and anorexia. While the older glandular products may be of little value,—such, for instance, as corpus luteum or ovarian extract,—there does seem to be some merit in the newer follicular hormones known to us under their various trade names. It is unfortunate that they are so expensive. With the restoration of normal menstruation, much of the nervousness disappears.

Increased sexual desire, due not to disease but to idleness and superalimentation, with its repression, is a troublesome factor in both sexes.

Thyroid disease is seen at times with tuberculosis, but it is more often mistaken for it, because of nervousness, asthenia, loss of weight, accelerated and irritable pulse, night-sweats, slight fever, and even cough. A combination of calcium with iodine seems to be helpful when the two diseases coexist.

Before considering actual mental disease, we should think of those conditions which are more common and which, if neglected, may lead to the former or at least nullify all our treatment. These are the anxiety states, such as homesickness, fear and worry; and the greatest of these is worry. In some cases it is an expression of the general nervous

condition which may have helped to inaugurate tuberculosis. Frequently it is simply an accompaniment, with little reason for its existence. However, it does occur in those of sanguine temperament, from such sufficient causes as financial stringency, disagreement with partners who are managing the patient's business, neglect on the part of the family to keep up correspondence, or fear of the consort's infidelity. Here, it is necessary to gain the patient's confidence to the extent of getting the entire matter "off his chest," and then to help as far as possible by taking appropriate action. A useful measure is to send a report home to the effect that the patient appears to be "slipping somewhat," due apparently to something on the mind, the details of which the writer does not care to know, but suggests that the situation be promptly adjusted so that the patient's progress toward recovery may continue.

Actual fear, while not as common as worry, is present in some patients, as in those who have an old fashioned horror of the diagnosis, or who have witnessed or learned of the death of another patient; or in those who suspect the spread of their infection or the development of complications. Such anxiety states may cause, or result from, endocrine imbalance,—an increase of adrenalin or sugar in the blood, with consequent deleterious effect.

Homesickness is often a serious obstacle to improvement, interfering with two of the fundaments of the "cure,"—rest and feeding. It may be ameliorated by the companionship of other patients of the same age and tastes who have gone through the same experience and are nearly well, affording diversion and encouragement. Books chosen for their particular appeal to the individual are helpful here; also the radio and, if permissible, knitting and certain other handicrafts.

Success here, and often in the entire management of the case, may depend upon where the patient is placed upon arrival. When one is obliged to make the necessary practical arrangements for the accommodation of new patients, the latter are found to be quite decidedly of one or the other of two kinds. There are those who wish to go to a quiet place where they will not have to meet anyone, whether other patients or "churchly" visitors, and there are those who, not only for financial reasons but because of their essential temperament, actually prefer to join a group "sight unseen" because they would "simply die without company." We have here our old friends of the psychologist, the introvert and the extrovert. This brings up the question as to whether or

not the so-called "shut-in" personality becomes intensified when actually shut in physically. Naturally, he may be, and such accentuation may increase morbid tendencies. However, it has been my observation that such persons make a better adjustment to the situation than their more gregarious brothers or sisters who cannot be happy without their persiflage, their baseball talk or their bridge games.

Except for terminal euphoria, the writer has had very little personal knowledge of actual mental disease occurring in the tuberculous, in an experience of twenty-seven years among various classes of people, including Latins, Slavs, Celts and Jews of the industrial centres, with their characteristic emotional patterns and the hundred per cent Anglo-Saxon of the South with, often, his religiosity and childish exaggerations.

Some patients of unstable temperament, who may have had little mental or nervous disturbance while engaged in a certain amount of physical and social activity, resent the restrictions of "the cure," and, if potentially psychotic, may actually break down mentally. Such possibilities were recognized by the government as far back as fifteen years ago in its policy of assigning a specialist in neuropsychiatry to every large tuberculosis hospital. (And the frequency with which the insane become tuberculous was recognized by the assignment of at least one tuberculosis specialist to each neuropsychiatric hospital.) The duty of the neuropsychiatrist was to maintain the morale of such patients as those described, by gaining their confidence and using appropriate psychotherapy, as well as to treat toxic delirium and to recognize promptly such manifestations of organic disease as symptoms of meningitis.

In a chronic disease with such troublesome symptoms as persistently recurring cough and, occasionally, agonizing pain, it is obvious that care must be exercised in the administration of opiates. The danger of addiction to codein, however, considering the extent of its use does not seem to be very great, and, if established, this is overcome usually without serious difficulty. A recent product with a fanciful name, however, has proved to be quite pernicious in my own experience. While it is supposed to be superior to morphine or codein, I have seen it produce almost unbreakable habit-formation within a comparatively short time.

I believe that there is more troublesome drug addiction than that involving narcotics in connection with sleep-producing drugs of the coal-tar or barbital group. In the early days of prohibition veronal was used

deliberately to produce intoxication, habitues deriving about the same effect as from alcohol. With recent reports of profound anaemia resulting from the use of barbital, and witnessing four attempts at suicide, one of which was successful, it seems very inconsistent that physicians and druggists should be checked up so strictly for prescriptions containing a little codein, when any layman may purchase a lethal amount of any of the barbital products for a nominal sum.

Now let us review briefly a condition with which most of us, unfortunately, are familiar and which has a definite organic lesion as its cause,—meningitis. The tuberculous variety may be preceded by increasing irritability and malaise; or it may start suddenly with intense headache, basal, frontal or general, persisting in spite of all medication and usually accompanied by explosive vomiting, without relation to food, and by fever. Muscular rigidity follows, especially of the neck and back. The patient may lose consciousness or become delirious, with screaming. Kernig's sign is usually present. Obstinate constipation is a feature. Children are more commonly attacked than adults, and it is often an expression of a general miliary involvement. The spinal fluid may be clear or slightly cloudy with an increased cell count, mostly of lymphocytes, and tubercle bacilli may be found. McCrae mentions the frequency of a history of a fall.

A similar but apparently much less common syndrome, which has proved to be quite puzzling, is that to which the term *meningismus* has been applied. This is characterized by the presence of several or all of the symptoms just mentioned, but in which the spinal fluid, except for increased pressure, is perfectly normal. According to Heiman (1), meningismus is synonomous with serous meningitis, which Antell (2) describes as follows:

> Serous meningitis is a term applied to a pathological condition which clinically resembles true meningitis, but in which the cerebro-spinal fluid is sterile. General serous meningitis may occur in the course of or following the general infectious fevers, such as pneumonia, influenza, rheumatism, etc. Cases have been reported following measles. Trauma, such as a blow on the head or a fall, may produce an attack. Since its first description by Dupre, in 1894, a certain amount of confusion exists in medical literature as to its nomenclature. Abt states that it would be far better if cases of meningismus were spoken of as serous meningitis. F. W. Law refers to it as aseptic meningitis, whereas Boyer uses aseptic meningitis only in cases that show signs of meningeal irritation which are produced by the introduction of foreign substances,

such as sera, into the spinal canal. Boyer attempted to simplify matters by differentiating meningismus from serous meningitis, meningismus being applied to cases in which the cerebro-spinal fluid is increased only in pressure; otherwise, chemically and microscopically, it is negative. He states, that although authorities still assert that in some cases of meningismus 30–40 or more cells may be found in the fluid, he nevertheless suggests that meningismus should refer to conditions in which the patient presents clinically the symptoms and signs of meningeal irritation, of variable intensity, but in which lumbar puncture reveals the fluid to be practically normal, except that it flows under increased pressure.

McCrae (3) says,

Serous meningitis is an ependymitis causing a serous effusion into the ventricles, with distention and pressure effects, it may be compared to the serous exudates in the pleura or synovial membranes. It is not certain that the process is inflammatory, and Quincke likens it to angio-neurotic edema.

Both children and adults are affected, the latter more frequently. In the acute form the condition is mistaken for tuberculous or purulent meningitis. There are headache, retraction of the neck and signs of increased intracranial pressure, choked disk, slow pulse, etc. Fever is usually absent, but there are cases with recurring paroxysms. In the chronic form the features are those of tumor—general, such as headache, slight fever, somnolence and delirium; and local, as exophthalmos, optic neuritis, spasms and rigidity of muscles, and paralysis of the cerebral nerves. Exacerbations occur and the symptoms vary in intensity. Recovery may follow and some reported cases of disappearance of symptoms of brain tumor belong in this category.

Kilduffe (4) commented as follows:

Concerning this condition—first described and named by Quincke—some confusion exists, both as to its occurrence and as to what conditions shall be so designated. Comparatively little is to be found regarding it in the literature, in all probability not because it is so infrequent, but because, perhaps, it is not recognized or reported as such. It is possible that, were it looked for, the condition would prove far from infrequent. Some confusion appears to exist, also, as to the terminology, the terms "toxic meningitis" and "sympathetic meningitis" being applied to it; although, if we define it to mean simply a state of irritation without a definite inflammatory reaction, the term meningitis serosa is probably to be preferred.

Strauss (5) noted that, "The cerebro-spinal fluid may react in the presence of a nearby suppurative process and show turbidity in the fluid, and an increase in pressure, in albumin and in cells, but without the

presence of bacteria. Early signs of meningitis may be present. This condition has been termed meningitis sympathica."

In 1925, Wallgren (6) of Sweden described a "new infectious disease of the central nervous system" resembling tuberculous meningitis, to which he gave the term aseptic meningitis.

In 1929, Viets and Watts (7) of Boston reported five cases of acute aseptic lymphocytic meningitis, lasting from three to six weeks, with recovery without paralysis.

Armstrong (8), of the United States Public Health Service, in animal experimentation with material from the St. Louis epidemic of encephalitis (1934), reported the discovery of a filterable virus which caused lymphocytic choriomeningitis and probably the same factor responsible for the cases of Wallgren, Viets and Watts. This work was confirmed by Rivers and Scott (9) of the Rockefeller Institute, in 1935, and by Findlay, Alcock and Stern (10) of Edinburgh, in March, 1936.

According to Greenfield and Carmichael (11),

it is usual to class meningeal inflammation and irritation as:

(1) Septic meningitis, when pus cells and organisms are present in the cerebro-spinal fluid.

(2) Serous meningitis, when a clear fluid contains an excess of cells but no organisms.

(3) Meningism, when the fluid is normal.

This classification rests more on clinical than on pathological grounds, chiefly in fact on the observation that in cases of types (2) and (3) the symptoms subside rapidly after lumbar puncture. It will be remembered that this is also true in mumps meningitis, and usually in typhoid meningitis, but when the cause of the meningitis is known, the disease is not classed as serous meningitis. "Meningism" is indeed a purely clinical term, and its relationship to any morbid conditions of the meninges is extremely vague. . . . The reason for the excess of cerebro-spinal fluid in these cases is not altogether clear. We can no longer accept the suggestion inherent in the name "serous" meningitis, that the fluid is poured out by inflamed meninges. If there is excessive production it must be due to alterations in the intracranial venous pressure, and naturally any sinus thrombosis would give rise to this. It seems likely, from the beneficial results of lumbar puncture, that in the majority of cases there is no excess in the formation of cerebro-spinal fluid, but rather a defect in its absorption.

In Boyd's (12) Pathology of Internal Diseases, we find that "in serous meningitis there are no bacteria and the sugar content is normal. The cell count may be normal or somewhat increased. In young children

there may be all the symptoms of acute meningitis, but the only change in the fluid may be a marked excess, quickly relieved by lumbar puncture." In the same work, under tuberculous meningitis, the spinal fluid is described as "clear or slightly milky, a web of fibrin forms on standing, there is a well-marked lymphocytosis with a varying number of polymorphonuclears, the protein is considerably increased, the sugar is low, though usually not absent, the chlorides are lower than in any other condition, tubercle bacilli can be found if the search is sufficiently prolonged."

The following case is reported as an illustration of the difficulty which exists in the classification of such phenomena as those which have been described. It suggested at first a distinctly organic or pathological process, but later, features which strongly suggested hysteria were superimposed:

G. F.; white; female; student; age 20. Admitted to sanatorium May 26, 1935, with diagnosis of tuberculosis; pulmonary, chronic, active, moderately advanced; referred by her family physician, with the significant remark that "her condition was that of one who was completely apathetic." Her history was irrelevant except for dysmenorrhoea, and for five years confinement in an orphanage, where she was required to do a certain amount of menial work and learned to be evasive and deceitful. She was ordered on bed-rest, but soon became notorious for breaking regulations and was out of bed a great deal, visiting other patients and behaving in a rather silly and unresponsive manner when spoken to about it. In September she developed symptoms of appendicitis, which had been smouldering for some time, and was operated on. About two weeks after operation she was out of bed and heard someone coming, whom she thought was the surgeon. She ran for her bed and slipped on the waxed floor, striking on her buttocks with considerable force. She said nothing about this accident to any of the medical staff and did not mention the pain which followed, but it was noted by another patient who reported it to the nurse. About a week later, on the evening of October 15, during rounds, this patient was found to have a peculiar flush of the face, deeply livid and extending over both cheeks and the bridge of the nose in the pattern suggestive of erysipelas. There was, however, no marginal elevation above the surrounding skin and no fever. As usual, she replied in monosyllables, to the effect that she was not feeling so well, but nothing new was found in either chest or abdomen. Passing along to other patients, the examiner was recalled to the girl's bed ten minutes later, to observe a convulsive seizure in which the extremities were all held stiff, fingers out straight and the head drawing back slightly. The patient appeared to be unconscious. This

condition persisted for a half-hour, when morphine and atropine were given; a special nurse was assigned for the night; and more morphine and atropine was administered during the night. This resulted in some relaxation, but the next morning there was vomiting, free perspiration and marked stiffening of all limbs and retraction of the head and shoulders, with apparent unconsciousness. A tentative diagnosis of tuberculous meningitis was made. A lumbar puncture was done the same evening, and the spinal fluid gushed out under considerable pressure but was found to be perfectly normal. The patient then became conscious and relaxed, but the next day there was a return of the bodily rigidity and vomiting, with much restlessness and moaning. The patient became very weak and required stimulation; this was followed by screaming and crying which needed sedatives. She then improved somewhat but, on the nineteenth, rigidity and unconsciousness again became so marked that another spinal puncture was performed. Learning of the fall, the possibility of traumatic meningitis occurred to us. Again the pressure was above normal, 10 mm. + (Hg); reaction, alkaline; sp. gr., 1.009; cell-count, 3 per cmm.; albumin, 0; sugar ++; Gram's stain negative; no tubercle bacilli found; quantitative sugar, 62.38 mgm.; quantitative protein, 41.5 mgm.; colloidal gold, no curve; chlorides, 728 mgm.; cultures sterile; globulin negative; Wassermann negative. In other words, these findings were practically normal. (Boyd (12) has found the estimation of the chlorides to be the most valuable of the chemical tests, the normal figure being from 0.72 to 0.75, falling in tuberculous meningitis to 0.65 or 0.60 or even 0.50, and seldom giving a reading above 0.65 per cent in tuberculous meningitis.)

This puncture was followed by improvement, but with considerable backache; and, on October 24, another spinal puncture was done because of a return of meningitic symptoms. The patient then became very quiet and comfortable and was able to take more nourishment than previously, which had been very little.

She then got along fairly well until about a month later when she became very angry because a nurse discovered that she had heated her thermometer to 103° while her temperature was actually normal. The patient overheard the nurse's report, and shortly afterward developed opisthotonos to the extent of indicating another spinal puncture, which was done, and the examination of the fluid again proved it to be perfectly normal, including the cell count. She improved after this to the extent of being given bath-room privileges, but a month later again developed symptoms. This monthly periodicity was suggestive, and the history of dysmenorrhoea was remembered, together with the patients peculiar mental make-up, and it was decided to treat the case as one of hysteria. She wanted a spinal puncture, but it was purposely withheld, and she got along just about as well on the administration of bromides and some morphine.

Her pulmonary condition was not adversely affected, and she left the sanatorium for economic reasons after two or three weeks of further observation, during which she had no return of the nervous phenomena. Recent reports from her home are to the effect that she is fairly well and has had no more nervous "spells."

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A COMPOSITE BLOOD CHART AS AN AID IN THE CONTROL OF THE TREATMENT OF TUBERCULOSIS[1]

HENRY C. SWEANY, INGRID STROM AND WILMA CANNEMEYER

For several years we have been working to perfect a blood chart for use in helping to determine the progress of tuberculous patients. This has been attempted because of the general agreement of haematologists that there is a change of the quality of the blood cells incident to a change in the disease. The recent work of Sabin and her associates, as well as of others, has pointed out the important rôle of cytology in tuberculosis. As a result, the feasibility of a system of cytological control of tuberculous patients is suggested. Doan (1), Wiseman (2), Crawford (3), Medlar (4), Flinn and Flinn (5), and others of the more recent workers have pointed out specifically the changes in the blood brought about as a direct result of the varying aspects of tuberculous infection. In general, these authors agree that the increased lymphocytes are the early indications of quiescence and healing,—a very old idea; that the increase of monocytes indicates new tubercle-formation; and that the polymorphonuclears are indicators of abscess-formation: in addition to this, a "shift to the left" in the polymorphonuclears indicates a greater acuteness of the process. Wiseman (2) has even reported a parallel prognostic index in a corresponding "shift to the left" in the lymphocytes. The haemoglobin-bearing elements are also of significance, but there are no real issues concerning these factors, because anaemia always has been accepted as an unfavorable condition.

Objection may be raised against such a plan because any one set of figures may tell the quality and quantity of involvement, but will not tell the progress a patient is making. It has been pointed out by Medlar (4) that repeated examinations are necessary for such an opinion. This we have provided for in the chart so that a patient may be followed for weeks, months, or even years.

While we were experimenting with a workable cytological blood-

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

chart, we also thought it would be still better to include a few of the most significant blood chemical findings as well, and thus present a composite blood-chart that would incorporate blood findings that are easily gained and of the greatest significance so far as the prognosis of tuberculosis is concerned. As the sedimentation rate of the red blood cells has become of great use in determining the condition of the patient at any particular moment, and reflects roughly the degree of involvement, it has been added. Some of the most useful indices as observed in earlier studies (6) on tuberculous blood, were the changes in the serum proteins—albumin, globulin and fibrin. In the more destructive type of disease there is a depletion of the albumin and an increase in the more labile globulins, including fibrin. In studying a large series of blood chemical analyses, it appears that the fibrin is almost a function of the amount of actual tissue destruction going on at the moment. Likewise, the albumin-globulin ratio expresses a similar relationship. On account of this we have included these various factors in the chart.

The charts may be more quickly understood if explained in detail. The first column, beginning with "Alb.," represents one group of substances with the quantities or numerical ratios next to the right. They are charted as solid lines. The normal is represented by a heavy line in the column under the heading "normal." It is joined to the quantity obtained in the first analysis by another solid line, usually running diagonally. The rise or fall of this diagonal line reveals graphically the increase or decrease of the substance from normal. Then, by following out the line the rise or fall can be studied over a long period of time if so desired. The column headed "Glob." is expressed in figures in the last column and charted in the chart by the dashes. The normal is expressed as before.

Taking up each substance individually, the first horizontal band charts albumin and globulin in mgm. per 100 cc. of blood. The two lines are nearly superimposed if normal, but, as the disease becomes worse, there is an increase of the globulin at the expense of the albumin. This is represented in the chart by a crossing of the dotted line above the solid line and takes on the forms of a "scissors." The wider the blades of the scissors the worse the condition. Another similar pairing is made in the second horizontal band. In this case the fibrin, expressed in mgm. per 100 cc. of blood, is plotted by the solid line, and the albumin/globulin ratio (protein quotient) by the dotted line. This also forms a gradually opening scissors as the conditions become worse. In the third

horizontal band are charted the five principal types of white blood cells in order: total white blood cells (first dotted line); neutrophiles (first

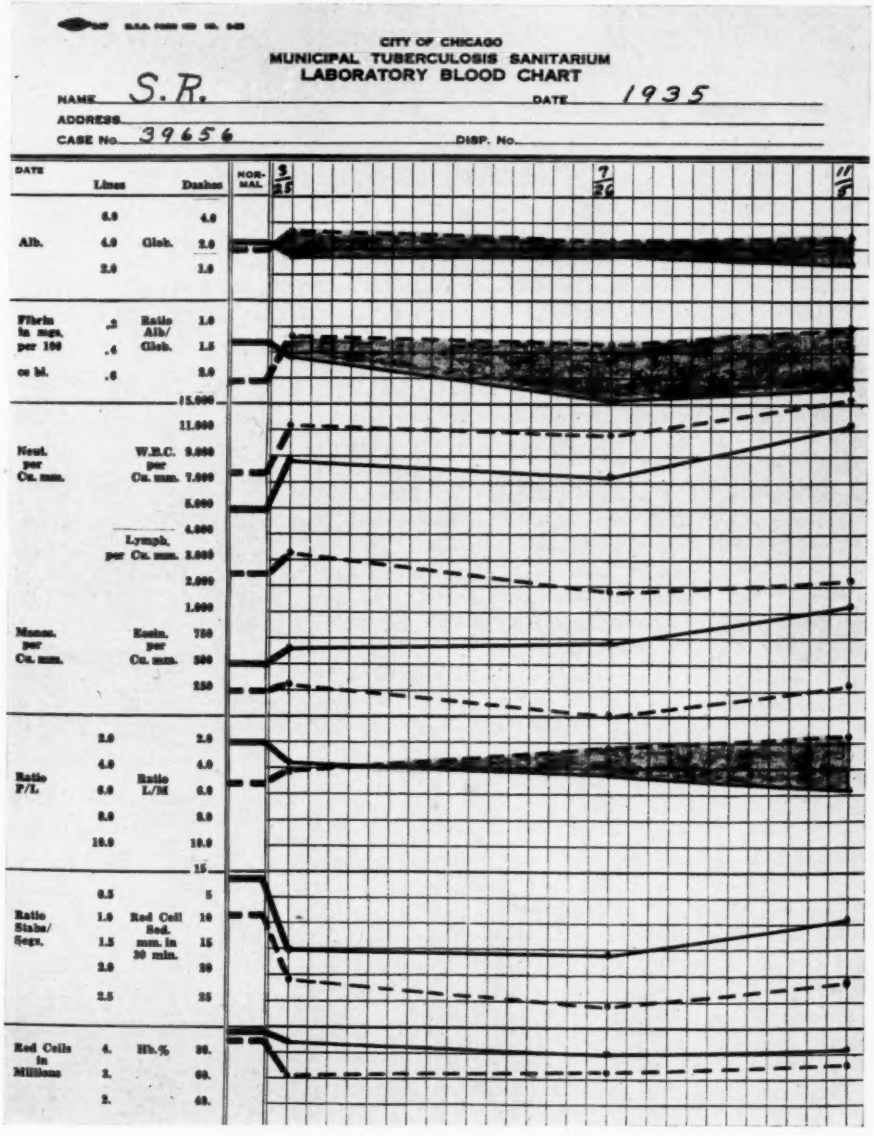

FIG. 1

solid line); lymphocytes (second dotted line); monocytes (second solid line); and the eosinophiles (the bottom dotted line). These are absolute

figures and may be expressed in percentages by dividing by the total white blood count and multiplying by 100. It seems more rational,

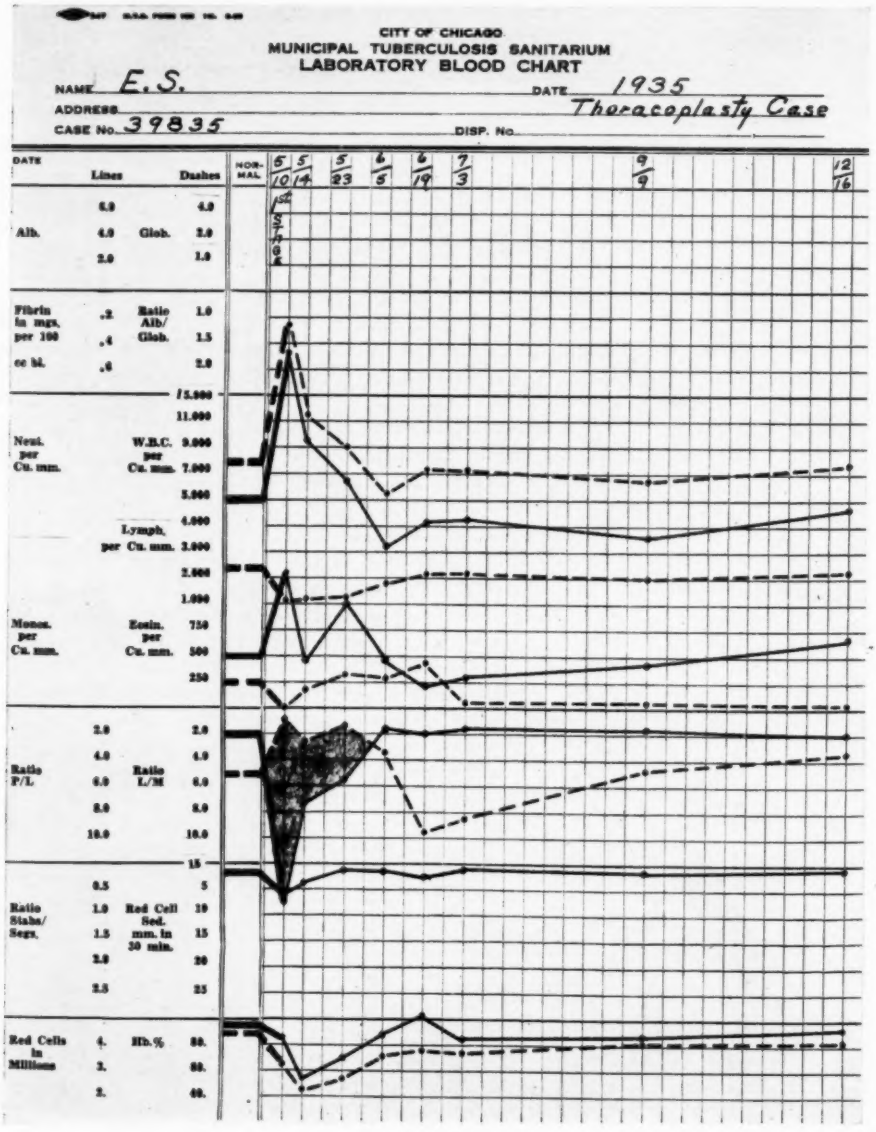

FIG. 2

however, to use the absolute figures and abandon the old method of expressing the values in percentages. In the fourth horizontal band are

shown the interrelationship of two sets of ratios; the polymorphonuclear-lymphocyte ratio (in the solid line) and the lymphocyte-monocyte ratio (in the barred line). They have been so devised that they reveal another "spreading scissors" as the disease becomes more unfavorable; but, if the lines become more divergent without crossing, the condition is more favorable or even normal. In the fifth horizontal band is shown by the solid lines the ratio of old or segmented leucocytes to the young or "Stab." forms. It is virtually a graphic Schilling index with only the two principal types of cell expressed. The dashes reveal the sedimentation rate expressed in minutes. It may be corrected for the degree of anaemia according to Rourke and Ernstene (7). In the last or sixth horizontal band are plotted the red blood cells in solid and the haemoglobin in barred lines. The figures for the red blood cells are millions and the haemoglobin is expressed in percentage.

Although this chart at first glance may seem complex, in reality it is not and offers a fine laboratory means of following the patient's condition.

Two charts are reproduced to illustrate in figure 1 a patient gradually failing (till death two months after the last analysis), and, in figure 2, one returning to normal after a thoracoplasty. In the former, there are the three groups revealing an appearance of an "open scissors" which predicts the fatal outcome. Note the rising polymorphonuclears and especially the rising monocytes with falling lymphocytes. There is a severe and stationary Schilling index, sedimentation rate, and red blood findings. In the second chart, there was a violent reversal of favorable indices at the time of the thoracoplasty operation, and a gradual return to normal. Note the rise of polymorphonuclears and monocytes and the fall of lymphocytes and eosinophiles during the severe stage. The blood chemistry was not performed on this case.

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TOLERANCE TESTS WITH FERRIC CHLORIDE ON ADVANCED TUBERCULOSIS PATIENTS[1, 2, 3]

VALY MENKIN

Previous studies by the writer have demonstrated that repeated intravenous injections of 0.25 per cent ferric-chloride solution in tuberculous rabbits are accompanied by an accumulation of iron in tubercles. Concomitantly with this accumulation the course of the disease in rabbits is definitely retarded. This has been shown in five independent series of experiments (1) (2) (3) (4) (5) (6) (7). The exact mechanism to account for this favorable effect has not as yet been elucidated. The accumulation of iron in tuberculous areas is as a rule demonstrable, not by microscopic test, but only in the gross when the tuberculous lung tissue is in contact with acidified $K_4Fe(CN)_6$. Experiments previously described (8) have shown that this is in large part due to a considerable loss of the iron, presumably during the "clearing" stage in the technique of microscopic preparation. Parallel to the deposition of iron in tuberculous foci, an intracellular iron pigment is also found microscopically to be deposited in the spleen, liver and bone-marrow. The pigment is indistinguishable from haemosiderin, but is not referable to haemoglobin degradation. It has therefore been termed *cytosiderin* (8) (9). The presence of this iron pigment in various organs, in addition to the nonpigmented form of the metal seen in the gross within pulmonary tubercles, renders it difficult at present to account adequately for the beneficial effect of $FeCl_3$ in tuberculous rabbits. The consistent experimental results, involving five independent series carried on for a period of five years, are now based on well over 100 rabbits and are summarized accordingly in table 1.

The consistency of these results suggested the possibility of clinical application. It has previously been reported that the intravenous

[1] From the Department of Pathology, Harvard University Medical School.

[2] Aided by a grant from the Committee on Therapeutic Research and the Committee on Scientific Research, American Medical Association; the Milton Fund, Harvard University; and the Proctor Fund of the Harvard Medical School.

[3] A preliminary report of this study was read before the 15th International Physiological Congress, Leningrad, August 16, 1935.

injection of ferric chloride, in concentration of 0.25 per cent, is irritating, producing local thrombi at the site of repeated inoculations in the ear-veins of rabbits (2). There was, however, no evidence of their propagation. It was believed that preliminary clinical tests with ferric chloride should be set up, in order to determine the tolerance or toxicity of this salt before attempting rigidly controlled human tests. The object

TABLE 1

Summary of studies on effect of ferric chloride in tuberculous rabbits

SERIES	RESULTS PUBLISHED IN	DOSE OF VIRULENT TUBERCLE BACILLI	ROUTE OF INOCULATION OF VIRULENT BACILLI	TOTAL NUMBER OF RABBITS	AVERAGE SURVIVAL TIME		INCREASE IN SURVIVAL TIME OF EXPERIMENTAL ANIMALS
					Control animals	Experimental animals	
		mgm.			*days*	*days*	*per cent*
1	1932	0.001	Intravenous	16	61	109	78
2	1933	0.001 (appx.)	Intravenous	20	94	135	44
3**	1936	0.01	Intravenous	19	84*	133	58
4	1934	0.05	Subcutaneous	10	130	246	89
5***	1934	0.05	Subcutaneous	10	81	198	144
Average					90	164	82
Total number of rabbits				75			

Series 6 (1933): Sixteen tuberculous rabbits killed between 45th and 79th day of the disease. Extent of tuberculous involvement in lungs of experimental animals considerably less than in controls.

Series 7 (1933): Nineteen tuberculous rabbits killed between 35th and 108th day of the disease. Tubercle bacilli inoculated subcutaneously. Experimental rabbits showed definite retardation in spread of the bacilli as evidenced by extent of lesion, particularly in the lungs.

Total number of rabbits in series: 110.

* Average survival time in nonvaccinated group of 8 control rabbits was 39 days.

** This group received a preliminary vaccination with *BCG*.

*** This group received preliminary vaccination with Cernay strain.

of this note is to report such preliminary tests on 5 human patients with advanced tuberculosis. When this plan of investigation was presented before Doctor Donald S. King by Professor S. B. Wolbach and the writer, Doctor King kindly placed several far-advanced patients at my disposal at Channing Home, Boston. The patients selected were not individuals in whom it was expected that ferric-chloride administration could possibly bring about any improvement. Most of the intravenous

injections were performed by Doctor David Halbersleben, whose valuable assistance is herewith acknowledged.

The first case was that of a woman of 45, with a history of advanced pulmonary tuberculosis of at least one year's duration. When first seen by the writer she was highly emaciated and almost moribund.

The first intravenous injection into the anticubital vein consisted of 4.5 cc. of 0.25 per cent isotonic ferric-chloride solution. This was the concentration of the salt employed in the experimentation on tuberculous rabbits. This injection subsequently produced definite local thickening and tenderness to palpation of the injected vein. For this reason subsequent injections were made by diluting the original ferric-chloride solution in saline solution, so that the final concentration of the iron salt was 0.0625 per cent. Injections of 20 cc. each were made three times a week. The stock solution at first was kept in an Erlenmeyer flask on ice. Before withdrawal from the flask of the ferric chloride necessary for each injection, the stock solution was gently heated by allowing hot water to run along the walls of the flask. Eight intravenous injections were performed with this technique. Local thickening of injected veins recurred continuously. It was then noted that the stock solution, which had been gently heated preceding each injection, was of a deep yellow color and was not always perfectly clear. Subsequently this change was avoided by heating only the portion of the solution which was to be injected immediately. When this technique was used, the solutions proved less irritating. Seven more injections, using the newly developed technique, were made. The total amount of ferric chloride injected was equal to about one-quarter the amount administered to a rabbit. The patient ultimately succumbed to her disease. Autopsy revealed overwhelming tuberculous involvement of both lungs with extensive cavitation. The arm-veins showed definite local iron-containing thrombi with extensive canalization. Thorough gross and microscopic examination of organs showed no evidence (by the prussian-blue test) of propagating iron-containing thrombi anywhere. The evidence indicated that the patient's death was due to the massive tuberculous infection and was in no way referable, directly or indirectly, to the administration of ferric chloride.

The isotonic ferric-chloride solution employed in the other four advanced cases was prepared as follows: 680 mgm. of sodium chloride were added to 100 cc. of 0.25 per cent ferric-chloride solution in distilled water. This in turn was diluted by the addition of 300 cc. of physiological

salt solution, so that the final concentration of the iron salt was 0.0625 per cent. The stock solution was passed through a Berkefeld filter and placed on ice. Sterility tests on broth were performed; and, as a precautionary measure, about 20 cc. of this solution were injected intravenously into a rabbit's ear-vein. The stock solution was kept on ice and exposed to room temperature as little as possible. The dose to be injected was carefully poured into a sterile 50-cc. Erhlenmyer flask. The solution was gently heated to about room temperature by holding the flask under a jet of hot running water. Injections were performed slowly into the arm-veins. The veins selected were shifted, whenever possible, from one injection to another, so as to reduce local injury to a minimum. From two to three injections per week were given. The dose employed was from 20 to 30 cc., although at first some of the patients received somewhat lower dosages. The course of injections in 4 patients was maintained from two to four months.

Minor local thickenings of veins, sometimes accompanied by local tenderness and redness (especially if the material was injected into relatively small arm-veins) recurred, in spite of the technique described above. The degree and the frequency of local injury was, however, apparently diminished. Furthermore, the local thickening of vessels invariably disappeared to palpation within several days. It is important to point out that no untoward or generalized *systemic* deleterious effect was ever noted in any of the patients intravenously injected with 0.0625 per cent ferric chloride.

Although no favorable effect of the iron salt injections was expected in these far-advanced cases, it may be mentioned that, about one year following the beginning of this investigation (and eight months after cessation of the treatment), three of these 4 patients are clinically improved or are doing well. It must be remembered, however, that all these patients were receiving, in addition, pneumothorax treatment and at least one of them was also on quartz-lamp therapy. Consequently, on such a small series of far-advanced patients, receiving combined treatment, not only can no conclusion be drawn on the therapeutic effect of ferric chloride, but any such inference must at present be guarded and is therefore to be considered merely suggestive. A brief description of these 4 cases follows:

1: Miss S; 20 years old; advanced and progressive pulmonary tuberculosis of both lungs of three years' duration. Time of treatment, February 12 to June 29, 1935. Number of injections, 31. Total amount of 0.0625 per cent ferric

chloride injected, 685 cc. X-ray showed development of large left apical cavity during course of treatment. Although she had gained 4 lbs. during a period of four months following cessation of treatment, on March 1, 1936, the patient was found to be losing weight and definitely failing.[4]

2: Miss C; 23 years old; pulmonary tuberculosis complicated by intestinal involvement; has run a long and stormy course with considerable irregularity; condition was unstable at onset of treatment, February 23, 1935. Treatment

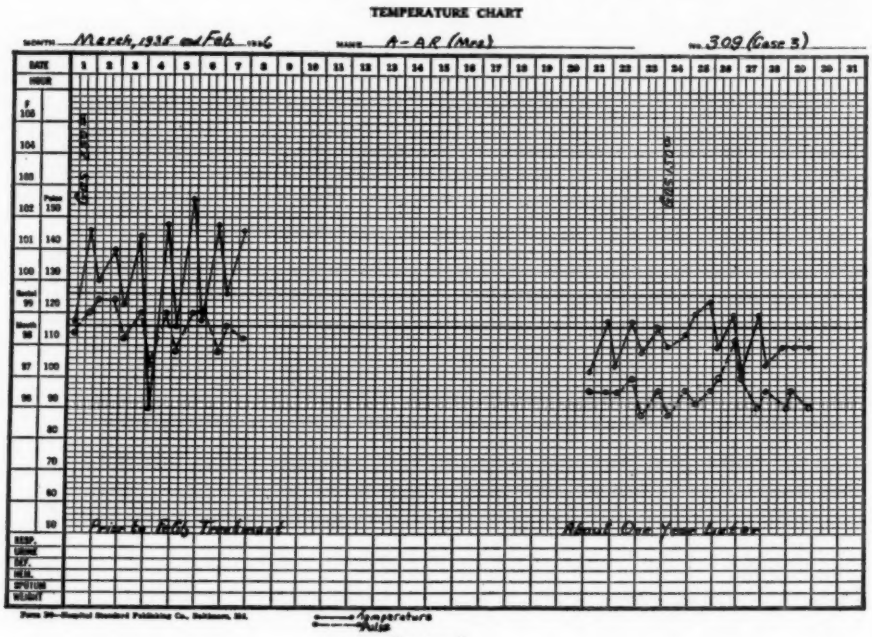

CHART 1

lasted until May 27, 1935; 27 injections in all; total amount of ferric chloride injected, 564 cc. Discharged as quiescent, August 1, 1935. Patient continued to do well (at least up to March, 1936, at the time of writing this report).

3: Mrs. A; 23 years old; advanced pulmonary case, involving both lungs, of at least two years' duration; patient had right pneumothorax with marked pleural reaction. Was running a swinging temperature at the time treatment with ferric chloride was started; temperature at that time reached peaks of 102° to 103°F.; pulse average around 110. Treatment began March 9, 1935,

[4] This patient was subsequently operated upon on two successive occasions. She finally succumbed in November, 1936 (about sixteen months after the cessation of the iron chloride treatment).

and ended June 27, 1935; 22 injections; total amount of ferric chloride injected, 511 cc. From February 1 to February 11, 1936, patient received four additional injections, aggregating 54 cc. of the iron salt. She is clinically much improved (March 1, 1936). Her X-ray shows progression in the uncollapsed lung. Her temperature is much better, in fact almost normal, not exceeding 99.5°F., as a rule. Her pulse averages around 95. She has gained 10 lbs. in the past year since treatment was instituted. Evidence of clinical improvement began in September, 1935, two months after cessation of ferric-

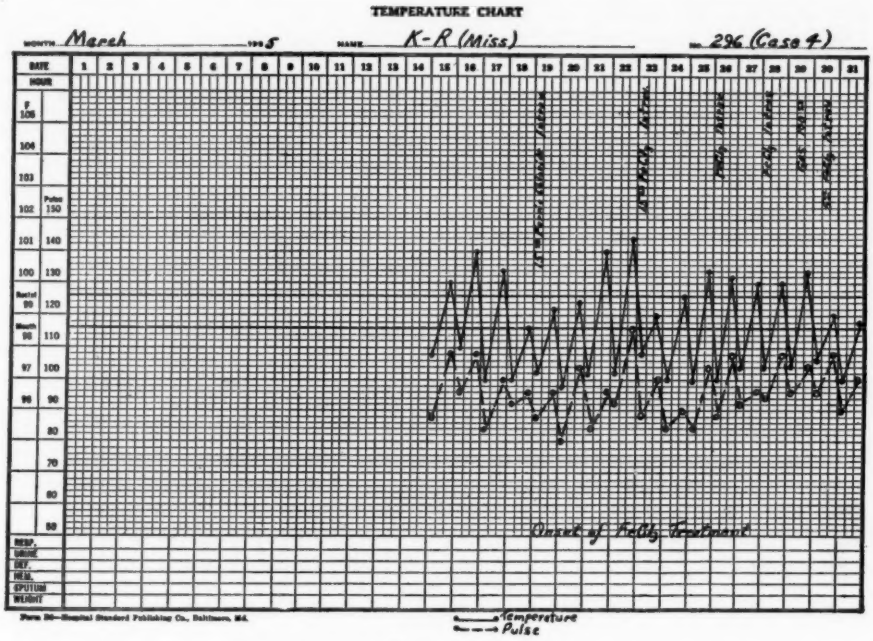

CHART 2

chloride treatment. Temperature and pulse records prior to $FeCl_3$ treatment and present temperature status (February, 1936) appear in chart 1. (See second addendum.)

4: Miss K; 24 years old; very sick with tuberculous pneumonia in the spring of 1934; pneumothorax was started in left lung, followed by marked pleural reaction. The right lung was not affected. At the time that ferric-chloride treatment was instituted, patient was running a swinging temperature and was very ill. She would reach peaks of 101° to 101.5°F. Pulse averaged 95 to 100. Treatment began March 19 and ended May 28, 1935; 18 injections; total amount of ferric chloride injected, 356 cc. Improvement in general clinical condition, temperature, and blood picture began very soon after onset of

ferric-chloride treatment. The patient has also been getting pneumothorax and quartz-lamp therapy. Her temperature in February, 1936, was normal, and her pulse likewise. She gained 25 lbs. between the onset of treatment in March, 1935, and March 1, 1936, shortly after which she was discharged from Channing Home. Temperature and pulse records at the onset of $FeCl_3$ treatment appear in chart 2. Her temperature and pulse-rate about one year later appear in chart 3.

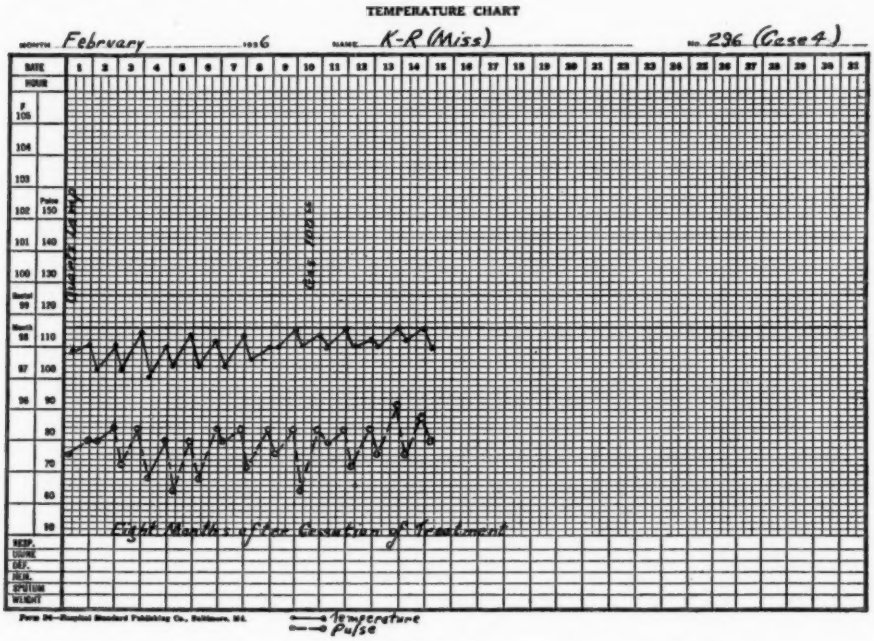

CHART 3

CONCLUSIONS

Several patients with far-advanced pulmonary tuberculosis have received repeated intravenous injections of isotonic ferric-chloride solution in concentration of 0.0625 per cent. The total number of intravenous injections performed was 116. No untoward *systemic* deleterious effects attributable to the iron have ever been observed in any of these patients. At the site of intravenous injection, especially in tiny veins, local and palpable vascular thickenings may occur with variable degrees of frequency. These small thickenings invariably and completely subside within several days. There has never been, in the cases studied, any evidence of anything simulating even in the remotest manner the propa-

gation of such local and temporary vascular lesions. The intravenous administration of the salt in the concentration used is evidently well tolerated by human beings. In view of these facts and of the consistent experimental findings on tuberculous rabbits coupled with the possible suggestion of clinical improvement in two of the 4 advanced cases of human tuberculosis reported in this paper, the opinion of the writer is that rigidly controlled and cautiously carried-out investigations on early or only moderately advanced cases of human pulmonary tuberculosis should be undertaken in order to determine whether or not this iron salt will yield favorable effects similar to those found on tuberculous rabbits. Of course, in order to arrive at a proper evaluation of ferric-chloride treatment, the initial clinical experiments should not be combined with any other form of therapy, but should be compared with results obtained from recognized types of treatment. It is believed that the present facts warrant such an investigation.

Special thanks are due to Doctor Donald S. King for allowing this study to be carried out on several patients at Channing Home, Boston, and to Miss E. Pelton, superintendent of the hospital, for her constant and unfailing coöperation throughout the period of this investigation.

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Addendum

Subsequent to submitting this paper for publication, a short series of rabbits was inoculated intravenously, each with 0.001 mgm. of bovine Ravenel tubercle bacilli. About 10 days later treatment was initiated by repeated intravenous injections of 0.0625 per cent of isotonic ferric chloride. This was continued (in about half of the animals) for 8 weeks. The total amount of ion chloride injected was considerably less than in the previous experimental series when the higher concentration of 0.25 per cent $FeCl_3$ was employed. Nevertheless, an essentially similar favorable trend in the course of the experimental disease, as indicated by the increase in survival time, was noted in the experimental group of animals. The three longest-lived control rabbits survived a shorter

period than the three longest experimental animals. An experimental animal was still alive 217 days after intravenous inoculation with the bacilli, whereas the longest control survivor succumbed 159 days after being infected.

Although a concentration of 0.0625 per cent of $FeCl_3$ was selected for the tolerance tests on humans, it is conceivable that a slightly higher concentration (perhaps even doubling this initial concentration) may be found, when cautiously administered, to be perfectly innocuous and perhaps more effective.

Second Addendum

Nine months after writing this report and when it was already in press (on December 2, 1936), this patient suddenly died of a severe haemorrhage localized at autopsy in the left lung. While the lungs, spleen and abdominal lymph nodes showed extensive tuberculous involvement, there was no evidence in the gross of any thrombosis or other lesion which might in any way be referable to the ferric chloride treatment which had been discontinued ten months previously.

MULTIPLE CALCIFICATION[1]

PAUL D. CRIMM AND J. W. STRAYER[2]

X-ray studies of multiple calcification reveal the predominating type of pathogenesis in pulmonary tuberculosis. A pathological study is naturally a prerequisite for an exact interpretation of any X-ray findings on multiple calcification, and Sweany (1) recently made an exhaustive study of the condition on cases selected from over 600 autopsies. He presented five principal classifications under which he explains not only the age and character of the lesion, but the mechanism of the process which produced them. Sweany's (1) classification is, of course, too technical for use in interpreting X-ray films. Thus, we employ the following tentative classification which includes only three groups: namely, bronchogenetic, haematogenous, and mixed reinfection. This classification can be applied to any group, and to either the primary or reinfection group. In an examination of the films of 3,218 cases, both children and adults, we selected for classification only those which presented six or more areas of calcification in the lung fields, not including tracheobronchial lymph nodes.

In radiograms which show a bronchogenetic type of mechanism of infection, the lesions are bilateral but asymmetrical. There is a greater variation in the size and shape of the lesions than in the haematogenous type. In general, the lesions are not nearly so numerous. Twenty cases, or 0.62 per cent, were classified in this group and were the result of bronchogenetic, bilateral seeding, as suggested by Huebschmann (2).

One can interpret a radiogram which reveals a haematogenous mechanism of infection as follows: the lesions are bilateral and symmetrical; round areas of calcification are more frequent than angular ones; the hilum contains calcified nodes similar to the lesion in the parenchyma; occasionally a single, large tracheobronchial lymph node is calcified. In this series of 3,218 cases, 16 or 0.50 per cent, were classified as haematogenous. It is interesting to note that 5 cases showed approximately the following number of calcifications: 255, 575, 666, 672, and 711, respectively.

[1] From Boehne Tuberculosis Hospital, Evansville, Indiana.
[2] Wm. Ross Sanatorium, Lafayette, Indiana.

The mixed reinfection group exhibits all sizes of calcification from small, angular lesions (seldom round) to large, crenated forms. There are often masses of calcification. This calcification is exogenous or endogenous in character, and may be haematogenous. The lesions appear bilaterally, or unilaterally and are asymmetrical in arrangement. Seventeen, radiograms (0.53 per cent) were classified in this group.

DISCUSSION

In studying the preceding types of calcification, only films containing more than 6 lesions were classified. We now discuss the same series of films, which showed one or more calcified lesions, from the standpoint of primary and secondary infection. We do not mean to imply that absence of visible calcification means absence of primary infection, but simply to record the frequency of occurrence of calcified tuberculous lesions as seen in this particular series of X-ray films. These 3,218 consecutive X-rays were taken at a tuberculosis hospital, which includes a children's hospital and an outpatient department.

Of 1,220 children, 619, or 50.7 per cent, had primary tuberculosis as evidenced by calcification in the lungs. It was deemed unnecessary to hospitalize any of the 619 cases more than thirty days. The fact that 50.7 per cent of children had calcification was due to the admission of many contact cases. Three were found to have had an inactive secondary infection.

Four-hundred and forty-seven out of 1,998 adults, or 22.4 per cent, had X-ray evidence of pulmonary calcification; 288 of the 447, or 64.4 per cent, without active disease, had only primary tuberculosis, as evidenced by the presence of pulmonary calcification. Six-hundred and ninety-four of the adults, or 34.7 per cent, had active disease; 159, or 22.8 per cent, of the 694 adults who had active pulmonary tuberculosis also had primary calcification.

In the light of current opinion on calcification in adults, one would expect a much higher percentage than that found in this series of X-rays. Although 64.4 per cent of the adults showing calcified lesions had primary tuberculosis without secondary infection, the limited number of cases forbids any statement as to whether or not a primary lesion, as evidenced by calcification, confers any immunity upon the already allergic individual.

SUMMARY

1. A tentative classification of multiple calcification is presented, which can be used for any age-group. Although presumptive information, such a study also reveals the predominant pathological mechanism in primary, secondary and reinfection groups.

2. In this series 53, or 1.64 per cent, showed multiple calcifications, that is, more than six lesions. Twenty cases, or 0.62 per cent, were bronchogenetic; 16, or 0.50 per cent, were classified as haematogenous; and 17, or 0.53 per cent, were of the mixed reinfection type.

3. In a series of 1,220 children (mostly contacts), 50.7 per cent had primary tuberculosis, as evidenced by pulmonary calcification.

4. In a series of 1,998 adults, 22.4 per cent had X-ray evidence of pulmonary calcification; 64.4 per cent of those having calcification had, as yet, not encountered a secondary infection.

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ORAL TUBERCULOUS LESIONS

CHARLES C. DARLINGTON[1] AND IRVING SALMAN[2]

REFERENCES

Based upon our knowledge of the literature on the subject of tuberculosis in relationship to the mouth, we will first summarize our general impressions. While the literature on tuberculosis is probably more voluminous and complete than on any other single condition or disease, that which we have found on tuberculosis in relationship to dentistry is, in comparison, meagre and less scientific. Tuberculosis of the tongue has received much consideration, some of which is excellent. There are some very interesting references which date back to the nineteenth century.

We shall now attempt to present in summary form our impressions of the literature on different factors related to our subject, grouping them as much as possible under special subheadings. These subheadings are divided into six groups. These groups are selected to show various kinds of reports or studies made. While all of them are concerned with tuberculosis and the mouth, only the last group, group 6, dealing with tuberculous oral lesions, has a direct bearing to the subject of this investigation.

We have not made an exhaustive review of the literature, but from that which we have made, we shall limit ourselves to those concerning tuberculosis of the mouth, and select at least one representative reference in support of each contention.

1: Experimental: A few of our oldest references are concerned with experimental work. Especially do we note references on (A) the introduction of tubercle bacilli or sputum containing tubercle bacilli into gingival pockets (1), or scarified gums (2), or mutilated teeth of laboratory animals (3), tending to produce tuberculous lymph nodes on the affected side; those on (B) the injection of debris or pus from the gums (2) or products of dental decay (4)

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[2] Oral Surgeon, Montefiore Hospital, and Department of Oral Surgery, New York University College of Dentistry.

from patients with tuberculosis, into guinea pigs, producing tuberculosis; and those on (C) the injection of tubercle bacilli into the tooth pulp of an ape, producing a rapid and severe generalized miliary tuberculosis (5).

2: Demonstration of acid-fast bacilli: Acid-fast bacilli were demonstrated from the mouth, as (A) the presence of acid-fast bacteria (some of which were apparently not tubercle bacilli) from the mouths of patients in whom there was no evidence of tuberculosis (6) (7); (B) the presence of tubercle bacilli from teeth, some of which were from children with tuberculous lymphadenitis (6) (8); and (C) the presence of tubercle bacilli from teeth of patients with latent or healed tuberculosis (6).

3: Dental caries as the portal of entry: That carious teeth may act as portals of entry for pulmonary tuberculosis has been claimed by several (9) (10) (11) (12) (13), while others claim a similar origin for tuberculous lymphadenitis (14) (15).

4: Bone tuberculosis: It is our impression that references to tuberculosis in relation to the bone structure of the mouth are scanty and confusing. In respect to this subject there are three types of reference, which are (A) reports of tuberculosis of the mandible (12) and of the maxilla (11), as resulting from previous dental caries; (B) attention called to indirect relationship between tuberculosis and chronic pulmonary osteoarthropathy, resulting in bony enlargements in the mouth (16); and (C) an extensive study and review of tuberculosis of the bones, comparing human and bovine types of organism, in which one case out of 665 was in the jaw (17).

5: Pyorrhoea, foci of infection, greater tendency to dental disease: Many statements, pro and con, especially in dental literature having to do with the following are encountered: (A) the presence of pyorrhoea in 90 per cent of patients with tuberculosis (18); (B) foci of infection, such as (a) septic tonsils and teeth, making the tuberculous patient more susceptible to haemorrhage (20), (b) diseased teeth, predisposing to tuberculosis and standing in the way of recovery (13), and (c) the influence of focal infection in relation to tuberculosis with special consideration of myocarditis (19); (C) a greater tendency in patients with tuberculosis to have dental diseases (21), as in (a) the production of Thompson's line, the relationship between caries and tuberculosis, and the frequency of Vincent's infection in tuberculous patients (22), and (b) pulmonary tuberculosis as predisposing to pyorrhoea alveolaris (2) (6), and (c) the special association of caries, cervical erosion, and gingivitis in tuberculosis (23) (24); (D) no unusual tendency to dental disease in tuberculous patients (6) (25).

6: Oral tuberculous lesions: As oral tuberculous lesions are our main problem we will give these references more careful consideration and divide them into nine subgroups.

A: Number of cases: From various locations, mostly tuberculosis hospitals or services, and others from departments of laryngology, statistics are given, calling attention to the rarity of mouth tuberculous lesions: (a) four or five lesions out of eight thousand laryngological cases (26); (b) four lesions out of twenty-eight hundred tuberculous patients (24); (c) seventy-two "buccal mucous-membrane" lesions out of five thousand tuberculous patients (27). Another reports no complications following one thousand teeth extractions in patients with far-advanced tuberculosis (28).

B: Location: Most of the reports in which the location of the oral lesion is stated, as said elsewhere, are tongue lesions. There are several references of isolated case-reports or small numbers of cases calling attention to mandible (12), maxilla (11), jaw (17), lip (27), alveolar process and glands (29), tooth-socket (23), gum, cheek and lip, premolar region (30). Several authors, in articles or in texts, state the locations as "Especially, tongue, gums, hard and soft palate" (30). Two reports of large series of cases are by:

1. Delavan (31) quoting Billings (114 cases)

Tongue	51
Pharynx	24
Mouth	22
Velum palati	8
Tonsils	4
Nasal cavity	5

2. Rubin (27) (72 cases)

Lip	6
Tongue	16
Cheeks, gums and floor	9
Pharynx	22
Tonsils	19

C: Method of infection: Considerable has been written as to whether tuberculous lesions in the mouth are primary or secondary. Here we have noted a tendency to believe that, the better the cases are investigated and the more evidence found, the more it is believed that their origin is secondary (6) (27) (31) (32). In considering how the tissues become infected, while various pathways of infection are mentioned, most authors stress infection via sputum (6) (31). Only one author emphasizes blood-stream and direct extension (27). Direct entrance through wounds or abrasions in the mouth is mentioned by a few (6).

D: Type of lesion: The type and clinical appearance of the lesions in cases of this kind have naturally received the most attention. Although we hear

most about ulcer, the following references show us at a glance the types of lesion encountered: Ulcer (6) (30) (31) (33)—ulcer, gumma, fissure, lupus, hypertrophic type of gingivitis, "mouse-eaten" appearance, tuberculoma, cold abscess and gingivitis (32), ulcerative "mouse-eaten" furrowed ulcerations, tuberculoma, lupus (27).

In relation to extractions, we find: Failure of wound to heal with subsequent ulceration (34), ulcer (35) (36), granuloma (23), and fistula with subsequent ulcer (31).

Laboratory procedures: Since certain laboratory aids, particularly tissue studies, offer us so much help in diagnosis we will consider three of them, namely, tissue examinations, smears and animal inoculations.

Tissue examinations: (*1*) *Histological picture:* No references to the microscopic tissue changes in tuberculosis are necessary. We will only emphasize that such responses are usually characteristic. There are, however, many references which emphasize that, while the microscopic picture of tuberculosis is characteristic, it is not absolute. In the mouth, especially, attention to this has been noted by some (6) (30) (32) (38). (*2*) *Demonstration of tubercle bacilli in tissue:* Attention has been called similarly to the importance of demonstrating tubercle bacilli in the lesion. The difficulties in obtaining positive results have also been emphasized in respect to oral material by some (32) (38).

Smears: The presence or absence of tubercle bacilli in the lesion, as well as the difficulty in demonstrating their presence in the oral lesions, have been noted on various occasions (6) (30) (32) (39).

Animal inoculations: The diagnostic importance of positive animal inoculations from suspected material needs no comment. With oral lesions, positive and negative results have been obtained (6) (30) (32).

The literature as to pain, sex, age and differential diagnosis can be summarized in a very few words.

E: Age: Most of the information as to age incidence points out the time of occurrence for such lesions to be between 20 and 60 years of age.

F: Sex: When sex incidence is noted, there seems to be a tremendous preponderance in males. Most of these records have to do with tuberculous lesions of the tongue (27) (31) (32).

G: Pain: Pain, especially, in the lesion early is emphasized by most writers (6) (27) (30) (33), but may not be a prominent feature (32).

H: Differential diagnosis: While there are many references dealing with the diagnosis and differential diagnosis of tuberculosis, syphilis and carcinoma,

most of them concern the tongue. Several have called attention to erroneous diagnosis of carcinoma or tuberculosis in the oral cavity (27) (31) (32) (38).

I: The mouth as first evidence of tuberculosis: Before concluding with references on tuberculous oral lesions it seems wise to conclude with a word on this phase. We know only a few reports in which the recognition of an oral tuberculous lesion antedated the recognition of the pulmonary tuberculosis (29) (30) (32).

SOURCE OF MATERIAL

In evaluating any study, full appreciation of the kind of material encountered, its source, and methods of investigation must first be known. In presenting such information, its limitations and advantages must be weighed. Fifteen cases are from Montefiore Hospital and twelve cases are from the New York University College of Dentistry Clinic, a total of 27 cases. All the former were hospitalized patients on the tuberculosis division of either Montefiore Hospital or Bedford Hills Sanatorium, the latter were clinic cases and, when first seen, were ambulatory. A painstakingly careful fact-finding study of their records is an integral part of the study. The records of the hospital cases are obviously much more informative than the clinic records. Many of the clinic cases did not have complete examinations, because they were seen at the clinic but once, failing to return for further investigations. Much the same can be said in comparing oral X-rays of the hospital and clinic cases respectively. Full-series preoperative oral X-rays were made on almost all of the hospital cases. The clinic cases did not have this advantage.

In comparing the sources of our cases it can be said that the hospital group presented a type of case that should be considered as advanced, whereas in the clinic group the type of case showed more variability. Further, in respect to the hospital group, it should be clearly understood that this study does not include all the tuberculosis cases in the hospital during the time that this study has been in progress, nor does it include every case that had a tuberculous mouth lesion.

The principal reason that influenced our case selection was an oral biopsy. While there were two exceptions to this, namely, cases 14 and 19 in which we did not have biopsies, these two cases were so characteristic that we feel justified in including them.

All oral tissues removed from tuberculous patients were not subjected to pathological tissue examinations. Neither was every tissue, removed from the cases presented, subjected to pathological study. Sections of

the teeth proper, removed from these cases, were not made except in case 13.

In the hospital group, autopsies were obtained in 4 cases. At these necropsies, on account of restrictions, head and neck organs were not examined in some, and in no case was autopsy material taken from the mouth. We are especially indebted to Dr. David Perla, Associate Pathologist at Montefiore Hospital, for his coöperation with biopsies and autopsies. Most of the hospital biopsies were done by him, and all the autopsies were done under his supervision. The remaining biopsies were done by one of us (C. G. D.), and a careful study and review of all of the biopsy sections by us constitute one of the most important phases of this study. In this study we attempted to carefully review the results of work done rather than saying just what should be done. The findings relative to negative sputum in these cases are included. In the tables, the time of positive and negative sputa, when known in relation to their operative procedure (oral lesion), is stated. Numerical studies of the number of tubercle bacilli (Gaffky counts), or studies as to the amount of sputum were not made. Sputum examinations, in relationship to the time of the oral lesion, also were not deliberately made.

Other clinical laboratory procedures, such as urinalyses, blood counts, blood chemical analyses and sedimentation rates, while done in most of the hospital cases, are not considered in this study. Animal inoculations, cultures, smears and demonstrations of tubercle bacilli in tissues from material of the oral lesions were not made except as indicated.

PATHOGENESIS

The primary problem of this study is pathogenesis. We shall limit ourselves to two phases, namely, the localization of the causative agent to produce the oral lesion and its subsequent course, and the production of a "characteristic" response in the tissue.

The localization of the causative agent in the mouth: In the development of any tuberculous lesion there are two major requirements which can be stated briefly as, first, and most essential, the presence of tubercle bacilli or their products (in the tissue), and, second, a loss of resistance or immunity.

In this study we shall confine ourselves entirely to certain problems connected with the first point, that is, the localization of tubercle bacilli or their products in the tissue. The second factor, a loss of resistance or immunity, will not concern us. Even in the consideration of the presence

of tubercle bacilli or their products in the tissues, we shall avoid discussion as much as possible, and summarize and emphasize only sufficiently to understand the special problem we have selected or undertaken to study and present. This problem is the method of development and extension (pathogenesis) of such tuberculous lesions in the mouth as we have encountered and investigated.

Whether the infection is primary or secondary is the first consideration. We believe that, the more studies (6) (31) (32) that are made on this subject, the more the evidence is accumulated (and studies of our own cases serve to confirm this opinion) that the bulk of these oral cases represent secondary infection. In the development or pathogenesis of a secondary tuberculous lesion it is necessary to transport tubercle bacilli from their primary site to the oral cavity, where they give rise to the secondary lesion. In the cases which we have investigated we feel that the evidence is irrefutable that all but two of our cases had active pulmonary tuberculosis at the time of development of their oral lesions.

The transportation or transplantation of tuberculosis is our main problem. In such transportation or transplantation of tubercle bacilli there are only four possibilities, one or more of which may be a factor in the same case. These four possibilities with brief comment or explanation are:

1: Mechanical extension: Under this heading transportation aerogenically or movements of a tissue, as well as transportation by such secretions as mucus, saliva, urine, faeces and sputum, have to be considered.

2: Direct extension: Extension of a tuberculous process with the tubercle bacilli and its products in direct continuity of tissue.

3: Via lymphatics or lymphoid tissue: This may be embolic or possibly a modification of direct extension. In the literature we have many references (40) that such extension is not always in the direction or flow of the lymphatics, in which cases it may be in the opposite direction, through blocking and might be thought of as a modification of direct extension.

4: Blood-stream: By way of a blood-vessel wall, at times, may be thought of as a part of direct extension, but, as the term blood-stream infection is ordinarily encountered, one thinks of the bacilli moving from one place to another in the blood-stream proper. In thinking of tubercle bacilli within the blood-stream three possibilities as well as probabilities must be considered: (a) bacteria gaining access to the blood-stream and living therein only a short period of time; (b) bacteria gaining access to the blood-stream and living therein a sufficient time to be carried from a point of entrance to a portal of exit into the

tissues; (c) bacteria gaining access to the blood-stream, and either continuously multiplying in the blood-stream or having a constant fountain of entrance, so that we think in both instances of bacilli being constantly present in the stream.

In discussing these methods of infection and extension in respect to the pathogenesis of tuberculous lesions in the mouth, we shall limit ourselves to comments on sputum, on the one hand, the case in favor of sputum as the agent, and the case against sputum as the medium, on the other hand.

Almost all regard sputum as paramount in the production of oral lesions, as the medium through which the tubercle bacilli are brought to the mouth and from which they leave to penetrate the mucous membrane and produce the tuberculous lesion.

While many arguments in support of this contention are advanced, especially do we hear of: (1) the presence of tubercle bacilli in the sputum, with the usual association of active pulmonary tuberculosis; (2) trauma, abrasions in the mouth; (3) ulcerations, gingivitis, etc.; and (4) extractions, as aetiological factors explaining the mode of entrance. Further, the following case report and quotations are illustrative of this view:

Zilz (*6*): Reports instance in which a lingual syphilitic placque was transformed by infected sputum into a tuberculous ulcer.
Appleton (*6*): "The origin is a secondary infection, implantation of tubercle bacilli from sputum upon persistent wound."
Ivy and Appleton (*30*): "Ulceration in the mouth undoubtedly is usually secondary to pulmonary tuberculosis, the infection being conveyed by the sputum. The tubercle bacilli are implanted in a region that has previously been the seat of a local inflammatory dental lesion, such as gingivitis or dento-alveolar disease."

In presenting the case against sputum, we have direct extension, lymph and blood-stream possibilities.

We are familiar with relatively few articles, which do not unduly emphasize sputum to the belittlement of other avenues as the medium of infection. Of them, there are only two to which we will refer. The first, by Finney and Finney (32), on *Tuberculosis of the Tongue*, states that, in the mode of establishment of the focus in the tongue, "implantation in traumatized areas, and direct extension of pre-existent lesions, seem to be the most common channels," and, second, there is an unusually excellent contribution on *Tuberculosis of the Buccal Mucous Membranes* by Rubin (27).

In discussing the relative immunity of the mouth in the production of oral tuberculous lesions, both of these authors mention, as some of the possible explanatory factors, "motion of organs, saliva, nature of tissues themselves, as striated muscle and stratified epithelium are known to possess a strong resistance to tubercle bacilli."

We feel that these factors also are evidence against infection of the mouth via sputum.

In additional support and explanation of nonsputum pathways of infection, we quote Rubin (27) who states, in comparing sputum and circulation as routes of infection:

> Certain facts favor the circulatory route as the more frequent of the two. This view is contrary to the generally accepted belief which favors direct inoculation with sputum as the method of infection. . . .
> Circulatory transmission of the virus explains the multiplicity of lesions and the clinical evidence of exacerbation of the disease in the lungs or of the extrapulmonic invasion that frequently becomes manifest at the same time. . . .
> Moreover, it seems that the nearer the parts involved are to the larynx the greater is the likelihood of laryngeal disease. . . . These observations suggest the possibility that the process in the larynx may become a source of further infection by contact and direct extension through the tissues. In this mechanism the lymphatics may play a part.

We feel strongly that our work substantiates Rubin's statements. It is an interesting coincidence that his studies were made at Montefiore Hospital, several years ago, whereas we, in our studies, most of them also from Montefiore material, and attacking our problem primarily from a dental viewpoint with different methods and different material, have independently reached a similar conclusion.

The production of a "characteristic" response in the tissue: It is unnecessary to give references to the microscopic picture of a tuberculous reaction. It is so characteristic and so much has been written about it, comprising as it does the basis of our entire knowledge of the histopathology of tuberculosis, that a very few words pertaining to the nature of such a picture should suffice.

The component elements in the microscopic picture characteristic of tuberculosis are epithelioid cells, giant cells, fibroblasts, lymphocytes, usually associated with caseation. Any and all tuberculous lesions have some "combination or permutation" (41) of these elements, especially a characteristic arrangement of concentric epithelioid cells called the

tubercle. Such were the main evidences in this study upon which the microscopic tissue reports of tuberculosis were made. As a rule, a diagnosis of tuberculosis is usually justified on the features just mentioned, even though smears, cultures, etc., are negative or not made.

Although we know that the classical Virchow picture only establishes a certain degree of probability of a tuberculous nature (42), and many other references (38) (43) (44) can be given that other conditions, especially syphilis, can simulate tuberculosis histologically, we feel that the evidence presented in the 24 cases justifies us in regarding these lesions as tuberculous in spite of the fact that smears, cultures, animal inoculations and tissue stains for tubercle bacilli were not made.

CLASSIFICATION

We have given considerable care and thought to the method to be used in our classification and arrangement of cases. Simplicity and clarity are best accomplished by a classification based on pathogenesis. In taking the pathogenesis into consideration, we are afforded an opportunity of grouping our cases so as to present the most formidable evidence in support of our conclusions.

Class 1: Tooth-apex or socket cases, 12 cases. In all of these cases the tuberculous lesion was present in relationship to a socket or tooth-apex.
Class 2: Mucous-membrane tuberculosis, 10 cases. Here we have 10 cases, in all of which, as our classification implies, one or more lesions were found in the mucous membrane of the gingiva, palate or tongue.
Class 3: Tuberculous osteomyelitis, 1 case.
Class 4: Tuberculous lymphadenitis, 1 case.
Class 5: Cases presenting difficulties in diagnosis, 4 cases. (Case 22 is also again presented under class 2.)

Class 1

Apex and socket: Class 1, our first main group, constitutes our largest number of cases, and, if we attempt to divide dental from nondental cases, these present definite dental problems. In all of these cases the lesions were located in relation to the tooth-apex or socket (depending on the presence or absence of the tooth).

We have divided these into two subgroups, A and B. The difference between these subgroups rests on the clinical absence of tuberculous granulations in the socket in subgroup A and the clinical presence of granulations in the socket in subgroup B.

In subgroup A (8 cases), in six of the eight, tissue was removed immediately postextraction from the socket area, and revealed tuberculosis histologically, while in the other two cases, the tissue was not removed from the socket until later.

In subgroup B (4 cases), after extraction and usually in a very short time, clinical evidences of tuberculous granulations, with failure of the socket to heal, were manifest. In most cases this was preceded by a purulent discharge from the socket.

The following case synopses of class 1 summarize the main oral findings as chronologically related to the oral tuberculosis. Brief notes concerning the patient's general condition, course and outcome are presented with each:

1: N. Y. U. C. D., male, age 30. Patient presented with swelling of one year's duration, which on X-ray showed cystic area. Tissue report showed tuberculous granulations and cystic changes. *Course:* Progressive. *Outcome:* Died $2\frac{1}{2}$ years postoperative, with diagnosis of chronic pulmonary tuberculosis.

2: M. H., male, age 58. Had loose tooth extracted. Tissue from socket reported as tuberculous granulation tissue. *Course:* Rapidly progressive. *Outcome:* Died one month postoperative, with diagnosis of bilateral fibrocaseous tuberculosis with marked cavitation, and diabetes mellitus.

3: M. H. and B. H., female, age 35. Had tooth with granuloma removed which histologically did not show tuberculosis. Two weeks later had roots of another tooth removed, tissue from socket of which showed tuberculous granulations. Uneventful healing occurred. The following week another tooth with cystic area removed. Smears from apex and root and tissue examination negative for tuberculosis. *Course:* Slowly progressive. *Outcome:* Living 11 months postoperative. Diagnosis of far-advanced bilateral pulmonary tuberculosis.

4: M. H., male, age 53. Two teeth removed, the roots of one of which showed apical granulation. Tissue report was "tuberculous granulations." Two months later, area normal. *Course:* Condition about the same. *Outcome:* Living 8 months postoperative. Diagnosis of pulmonary tuberculosis, arteriosclerosis, prostatic hypertrophy, and diabetes.

5: M. H., female, age 35. Tooth with granuloma surgically removed. Sections showed tuberculosis; followed by uneventful healing. *Course:* Patient doing well. Is gaining weight; no physical signs. Scant cough and expectora-

TABLE 1
Class 1

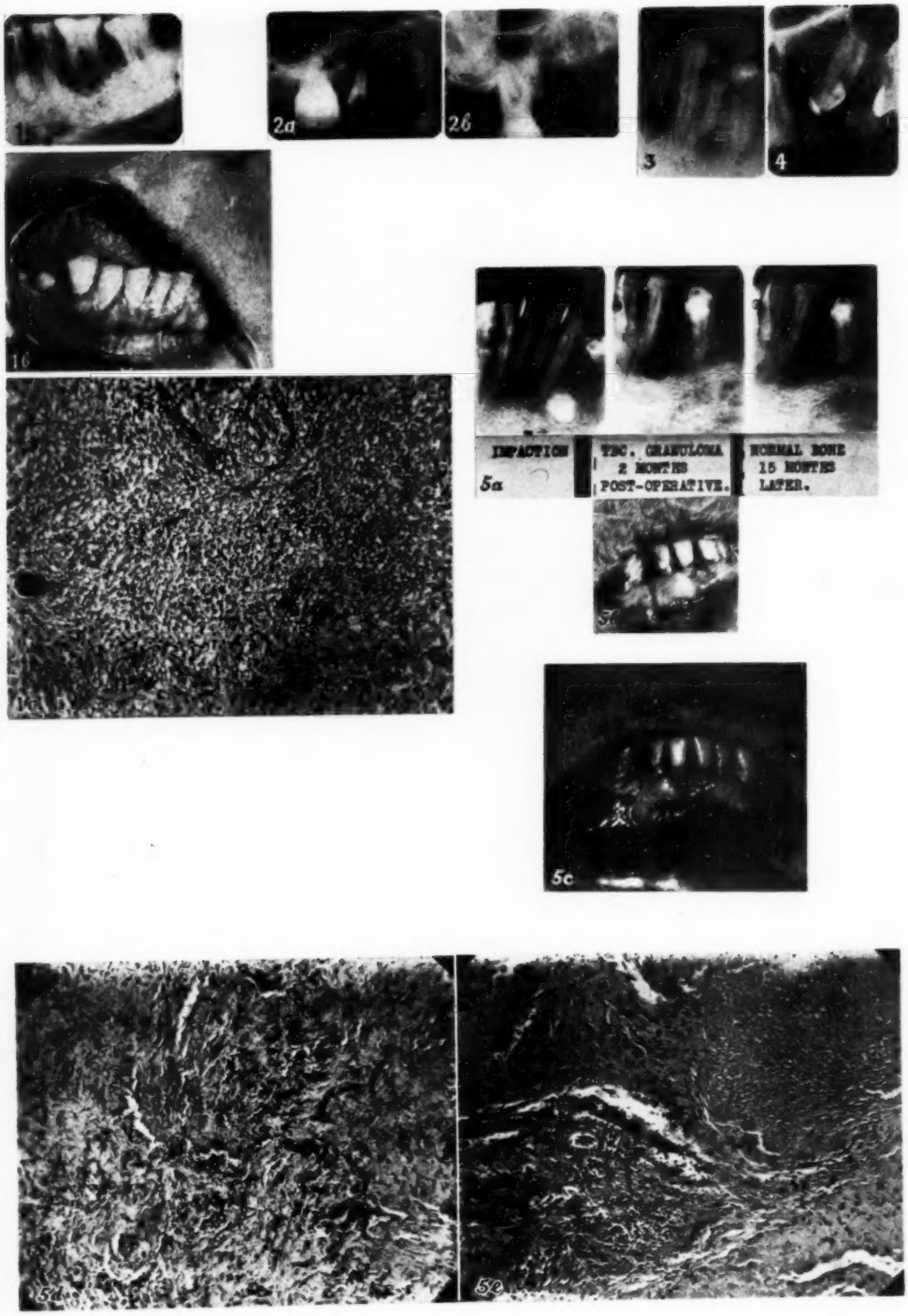
Number	1	2	3	4	5	6
Age	30	58	35	53	35	27
Sex	M	M	F	M	F	M
Location of oral lesion	?	$\overline{6}\|$	$\|\overline{8}$	$\|\underline{5}$	$\overline{4}\|$	$\underline{3\text{-}2}$
Pre-operative X-ray	Cyst	Bone destruction	Bone destruction	Granuloma	Granuloma	Impaction
Duration of oral lesion Past history	One year					
Since observation	2½ mos.?	†1 month	2 mos.	2 mos.	2 mos.	1 month
Outcome of oral lesion	?	*Still present	Healed	Healed	Healed	Healed
Sputum for tubercle bacilli	Unknown Operation Positive (2)	Positive (4) Operation Positive (1)	Negative (4) Positive (2) Operation Positive (4)	Positive (3) Operation Positive (3)	§Negative (4) Operation	Positive (4) Operation Negative (1)
Wassermann	Negative	‡Negative	Negative	Negative	Negative	Negative
Larynx	Negative	Negative	Negative	Negative	Negative	Negative
Present condition of patient	Dead 2½ years post-op.	Dead 1 month post-op.	Living 11 mos. post-op.	Living 8 mos. post-op.	Living 2½ years post-op.	Living 10 mos. post-op.
Duration of systemic condition	6 years	11 years	2¼ years	8 mos.(?)	4 years	2 years
General clinical diagnosis	Chr. pul. tbc	Bi-lat. fib.-cas. tbc with marked cavitation Diabetes mel.	Bi-lat. pul. tbc	Pul. tbc Art.-sclerosis Diabetes mel.	Sub-acute gener.-mil. tbc Healed peritoneal tbc	Chr. pul. tbc Diabetes mel.
Autopsy findings	Not done	Not done				

* Present at death.
† Up to death of patient.
‡ Past history of lues and anti-luetic treatment.
§ One week prior to operation.

TABLE 1

Class 1

6	7	8	9	10	11	12
27	42	20	27	29	50	50
M	M	F	M	M	F	M
3 2	$\overline{3-2}$ |	|6	$\overline{6}$ |	|6	|6	$\overline{7}$ |
mpaction	Granuloma	Bone destruction	Bone destruction	Negative	Alveoloclasia	Apical rarefaction
	2½ mos.	4 mos.	2 mos.	1 month	2 mos.	2½ mos.
1 month	8 mos.	†3 wks.	7 mos.	2 years	10 mos.	2 mos.
ealed	Healed	*Still present	Healed	Healed	Healed	Healed
sitive (4) peration gative (1)	Positive (1) Unknown Operation Unknown Positive (9)	No record	Positive (3) Operation Positive (4)	Negative (1) Positive (4) Operation Positive (2) Negative (1) Positive (4) Negative (1)	Positive (2) §Negative (2) Operation Positive Negative (2)	Positive (2) Operation Positive (1)
gative	Negative		Negative	Negative	Negative	Negative
gative	Negative		Negative	Positive	Positive	Negative
ing 10 mos. ost-op.	Living 2½ years post-op.	Dead 3 wks. post-op.	Dead 11 mos. post-op.	Alive 11 mos. post-op.	Dead 1 year post-op.	Dead 15 mos. post-op.
2 years	6½ years	2 years	7½ years	3 years	9 years	3½ years
. pul. tbc betes mel.	Bi-lat. pul. tbc	Pneumonia Pul. tbc	Tbc with cavitation	Ext. pul. tbc with cavitation	Bi-lat. fib.-cas. tbc Pott's disease Tbc laryngitis	Chr. bi-lat. ulcero-tbc
		Not done	Bi-lat. fib.-ulc. pul. tbc Tbc alveolar absc. Tbc jejunum Tbc adrenals		Chr. pul. tbc with cavitation Tbc pneumonia Healed tbc spondylitis Pott's disease Kyphoscoliosis	Not done


2a
2b
3
4
1c
5a
IMPACTION
TUC. GRANULOMA
2 MONTHS
POST-OPERATIVE.
NORMAL BONE
15 MONTHS
LATER.
5c
5d
5e

Figs. 1a–5e

tion. *Outcome:* Living 2½ years postoperative. Diagnosis of subacute generalized miliary tuberculosis, and healed peritoneal tuberculosis. This is a case of "chronic haematogenous, benign."

6: M. H., male, age 27, impacted tooth removed. Curetted tissue, socket showed tuberculosis. Uneventful healing followed. *Course:* Condition good; attending clinic. *Outcome:* Living 10 months postoperative. Diagnosis of chronic pulmonary tuberculosis and diabetes mellitus.

7: M. H., male, age 42. Impacted supernumerary removed surgically. Tissue showed bone destruction. About 2½ months later, symptoms appeared, which on X-ray showed granuloma in original impaction area. Granuloma removed, report of which showed granuloma with tuberculosis. Six days later, pin-hole sinus noticed at needle point (?) which only responded to intensive ultraviolet treatment. Eleven months later, area entirely healed with complete bone regeneration. Six months later, roots of another tooth removed, tissue report of which showed mild inflammatory reaction. *Course:* Condition about the same. *Outcome:* Living 2½ years postoperative. Diagnosis of bilateral pulmonary tuberculosis with cavitation.

Case 2

Fig. 1A. Preoperative X-ray, showing marked bone destruction $\bar{6}|$ region
Fig. 1B. Postoperative: photograph of $\bar{6}|$ socket showing exuberant granulation tissue in unhealed socket
Fig. 1C. Photomicrograph

Case 4

Fig. 2A. Preoperative X-ray of $|\underline{5}$, showing destruction around apex
Fig. 2B. Postoperative X-ray

Case 5

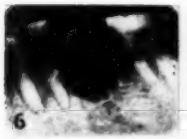
Fig. 3. Preoperative X-ray of $\bar{2}|$ and $\bar{4}|$, showing apical destruction of bone. Tissue from $\bar{4}|$ apex examined. Tissue from $\bar{2}|$ apex not examined

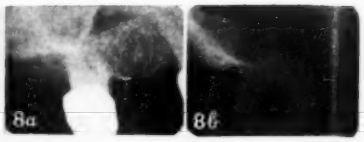
Case 6

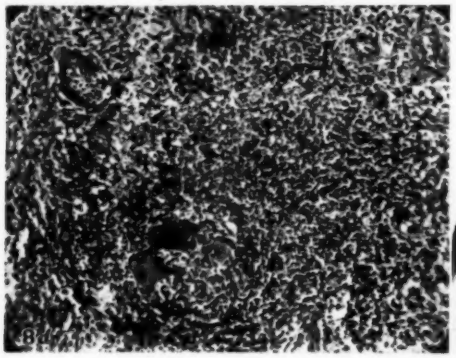
Fig. 4. Preoperative X-ray, showing impacted $\underline{3}|$ with marked bone destruction about crown of $\underline{3}|$ and apex of $\underline{2}|$

Case 7

Fig. 5A. X-rays
Fig. 5B. Photograph, showing sinus opening
Fig. 5C. Photograph, showing healed sinus
Fig. 5D. Photomicrograph: fibrous granuloma
Fig. 5E. Photomicrograph: tuberculosis







Figs. 6–11

8: N. Y. U. C. D., female, age 20. History of pain in lower left molar region and looseness of tooth, which was extracted. Five months later, single round circumscribed area appeared in the latter region with slight pain, discharge and progressive swelling. Tissue report showed tuberculous granulations. *Course:* Rapidly progressive. *Outcome:* Died 3 weeks postoperative. Diagnosis of pneumonia and pulmonary tuberculosis.

9: B. H. and M. H., male, age 27. About one year before hospital admission had tooth removed. On admission, X-ray revealed bone fragments in area from which, several months later, a purulent discharge was noted. About one year later, tissue from this area showed tuberculous granulations. Socket healed very slowly. *Course:* Progressive. *Outcome:* Died 11 months later with postmortem findings of bilateral fibroulcerative pulmonary tuberculosis, tuberculous alveolar abscess, tuberculous jejunum, and tuberculous adrenal (M. E.).

10: M. H., male, age 29. Tooth removed on account of extreme sensitiveness and no response to therapy. X-ray was negative. In about 2 weeks, exudate

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Case 9

Fig. 6. X-ray $\overline{6}|$

Case 10

Fig. 7A. Preoperative X-ray of $|\underline{6}$ showing no evidence of bone destruction about apices
Fig. 7B. Postoperative X-ray

Case 11

Fig. 8A. Preoperative X-ray $|\underline{6}$, showing evidences of no bone destruction
Fig. 8B. Postoperative X-ray
Fig. 8C. Photograph, showing granulation tissue in unhealed socket
Fig. 8D. Photomicrograph

Case 14

Fig. 9A. Photograph, showing tuberculous ulcer where $\bar{4}|$ was removed
Fig. 9B. Photograph, showing tuberculous ulcer in retromolar region on opposite side, where no tooth was removed

Case 15

Fig. 10. Photograph, showing mouse-eaten mulberry lesion of mucous membrane, upper right side

Case 20

Fig. 11. Tuberculosis of soft palate. (Courtesy of Dr. L. V. Hayes, New York City.)

of pus and granulations in socket noted. Surgical removal of granulations about one week later showed tuberculosis. *Course:* Slowly progressive. *Outcome:* Living 11 months postoperative. Diagnosis of extensive bilateral tuberculosis with cavitation.

11: M. H., female, age 50. Had two teeth removed, followed in 6 weeks by removal of two more teeth. Two weeks later, socket of one of last teeth removed showed tuberculosis. Wound followed by healing and remained healed. *Course:* Progressive. *Outcome:* Died 11 months later with clinical diagnosis of bilateral fibrocaseous tuberculosis, Pott's disease, and tuberculous laryngitis. Postmortem diagnosis of chronic tuberculosis with cavitation, tuberculous pneumonia, healed tuberculous spondylitis and kyphoscoliosis (neck organs not removed).

12: M. H., male, age 50. Had three teeth extracted, followed 3 weeks later by extraction of 3 more teeth and roots of another. Four days later, another tooth extracted. Two months after removal of roots, a purulent discharge noted from root area, followed in 3 weeks by removal of granulations from socket which showed tuberculosis. Two months later only slight depression at site visible. *Course:* Progressive. *Outcome:* Died 15 months postoperative. Dagnosis of chronic bilateral ulcerative tuberculosis.

In order to appreciate the salient factors brought out by our study of group 1, we may discuss representative cases.

Case 3 is quite typical of class 1, subgroup A. We select this one because, in contrast to most of the other cases in which one tissue examination was made, in this case three tissue examinations were secured. Also, we select it because examinations for tubercle bacilli in smears from the apices and socket were made, which also were not done on the other cases, except in special circumstances.

In this case we have three tissue examinations, all from tooth or root socket areas, from widely separated parts of the mouth. The second tissue from retained roots was the only one showing a tuberculous tissue reaction, although smears for tubercle bacilli were negative, from both apices and socket. Smears from apex and socket at the time of removal of the last specimen were also negative.

In keeping with these findings it is important to appreciate that, as far as we know, no case in this class had more than one tuberculous oral lesion, either more than one at a time or one following another.

Case 7 is quite atypical of this subgroup, but it is unusual and most interesting. An impaction in this case, giving no symptoms, was recog-

nized, bone from which histologically was negative 2½ months following its surgical removal, and symptoms appeared, when X-ray showed a granuloma in the original impaction area. Tissue sections showed a dense fibrous granuloma, the edges of which revealed a tuberculous picture. Six days postoperative, a pin-hole sinus was noted, which finally responded to heliotherapy. No biopsy was obtained from this sinus, and its exact nature was not proved. An important question in this case is when and how did this site of impaction become tuberculous? Was the tuberculous process there originally but not recognized, or did it develop following or as a result of the removal of the impaction? Also, by what pathway did the tubercle bacilli get to the area? While we feel in this case that the answers cannot be stated with certainty, if we compare this with other cases, we think that the infection was postoperative (first operation) and of haematogenous origin.

Case 11 is one of the best examples of class 1, subgroup B. A female, 50 years of age, gave a history of the removal of several teeth on two occasions, followed in two weeks by granulations in the socket, which were removed with subsequent healing.

Discussion

We have made two subdivisions of class 1 for the reasons given, and we believe that their pathogenesis is similar. We think that apex cases have a strong probability of later becoming socket cases if the tuberculous process at the time of removal of the tooth is not thoroughly eradicated. While we cannot deny the possibility that the trauma of extraction with or without curettage may serve to set up a *locus minoris resistentiae* to bring about the tuberculous reaction, we think the weight of evidence from our studies to be against this contention. As a means of prevention, therefore, of the tuberculous sockets, we strongly recommend thorough curettage and immediate pathological tissue examination of the socket in extractions on tuberculous patients who preoperatively show X-ray evidences of bone destruction.

While Fishberg (27) is quoted as having said, "although operations on the teeth and extractions are carried out frequently on tuberculosis patients, no heed is paid to the possibility of autoinoculation with tubercle bacilli, for by experience it has been found that such occurrences are extremely rare," we feel that the more progressive dental surgeons are aware of the possibility of autoinoculation with tubercle bacilli. In order to control postoperative haemorrhage, as well as to prevent

inoculation of sockets from sputum in tuberculous patients, immediate application of a gauze compress to the socket is done at Bedford Hills Sanatorium and Montefiore Hospital. Theoretically, the gauze may physically act as a barrier against the introduction of tubercle bacilli into the socket from the sputum or saliva. While we feel that blood and not sputum is a means of transportation of tubercle bacilli, we still recommend gauze packing of the socket for the control of haemorrhage.

Other factors worthy of comment on this group are reasons for extractions, relation to laryngeal involvement, and outcome as to lesion and patient.

Reasons for extractions: In this group, the reasons for extraction are known in almost all cases. More than one reason was present in some. In the largest number of cases X-ray evidences of bone destruction were present, while such subjective symptoms as pain and looseness were infrequently found.

Relation to laryngeal involvement: Of the 12 cases, while in one we have no information (case 8), the records of eleven state laryngeal involvement in two.

Outcome: We will consider the outcome under two headings: first, the patient and, second, the oral lesion. As regards the patient, of the 12 cases, six have died and six are living. Of the deaths, while two patients died quickly, four lived 11 months, 1 year, $1\frac{1}{4}$ years, and $2\frac{1}{2}$ years, respectively. Of the six living, the time since their operations have been 8 months, 10 months, 11 months, 11 months, $2\frac{1}{2}$ years, and $2\frac{1}{2}$ years, respectively. As for the oral lesion, in all but two of the entire twelve cases, this is healed or it had healed prior to death. The two patients with unhealed oral lesions died quickly, one month or less after operation.

Class 2

Class 2 is our second main group, in which the lesion or lesions are of the mucous membrane. While we did not have biopsies in two of these cases (14 and 19), histologically the remainder showed a subepithelial tuberculous reaction. In this group are 10 cases.

One of these cases was of a lesion of the tongue, two were lesions of the palate, and the remainder were located mainly or entirely on the gingiva.

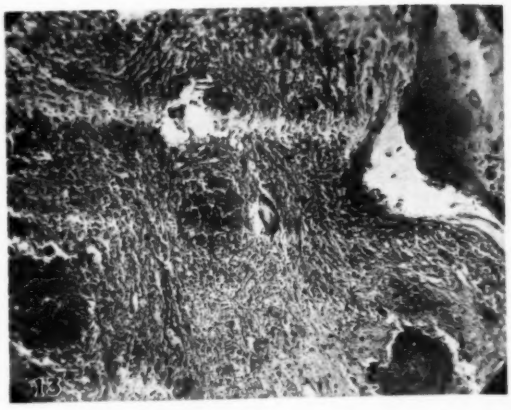
Most of these cases clinically appeared as angry red mulberry "mouse-eaten" areas, rather than distinct ulcerations which were present in three of the cases. One of these three, case 14, had two distinct separate ulcers, one in the retromolar region where no extraction had been made

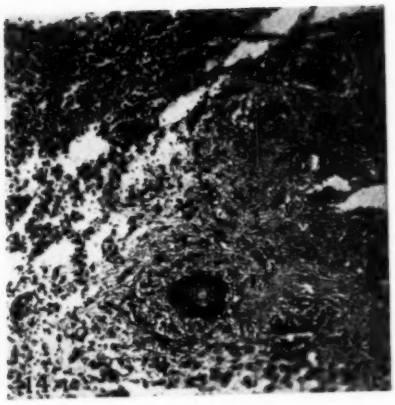
TABLE 2

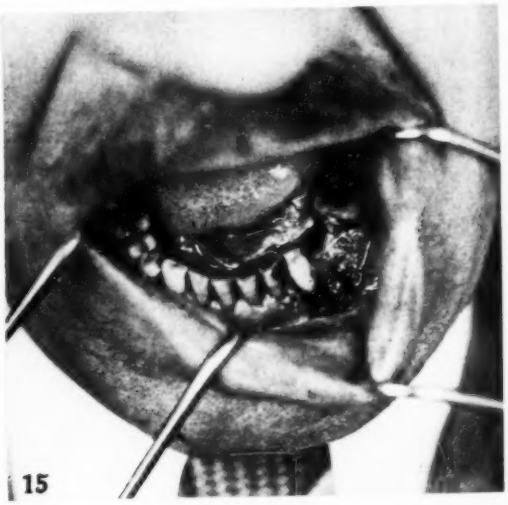
Class 2

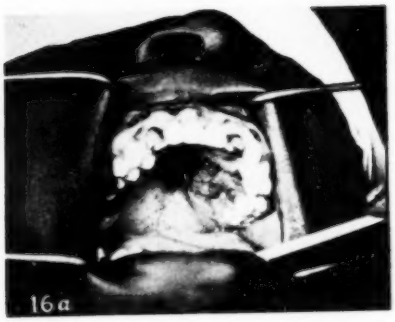
Number	13	14	15	16	17	18	19	20	21	22
Age	32	20	25	46	32	52	33	36	58	50
Sex	M	M	M	M	F	M	M	M	M	M
Location of oral lesion	$\overline{5\text{–}6\text{–}7\text{–}8}$	$\overline{4}$ | Retro-molar	$\underline{3\text{–}4\text{–}5\text{–}6\text{–}7\text{–}8}$	$\underline{2\text{–}8}$	?	$\overline{6\text{–}7\text{–}8}$	Soft palate	Soft palate	Tongue	$\overline{4\text{–}5}$
Duration of oral lesion Past history			3 years(?)		6 mos.	5 mos.		6 mos.	3 wks.	7 mos.
Since observation	†2½ years	†5 wks.	†5 mos.	†4½ mos.	No record	No record	†5 mos.	†3 mos.	†1 year	†2 mos.
Outcome of oral lesion	*Still present	*Still present	*Still present	*Still present	No record	No record	*Still present	*Still present	*Still present	*Still present
Sputum for tubercle bacilli	Positive	Positive	Positive	Positive	No record	No record	Positive (2) Negative (4)	Positive	Positive	No record
Wassermann		Negative	Negative		No record	No record	Negative	Negative	Negative	Negative
Larynx	Positive	Negative	Negative		No record	No record	Positive	Positive	Positive	
Present condition of patient	Dead 2½ years post-obs.	Dead 5 wks. post-obs.	Dead 5 mos. post-obs.	Dead 4½ mos. post-obs.	No record	No record	Dead 5 mos. post-obs.	Dead 3 mos. post-obs.	Dead 1 year post-obs.	Dead 2 mos. post-obs.
Duration of systemic condition	3½ years	1 year	4½ years	2 years	No record	No record	5 mos.	10 mos.	1½ years	9 mos.
General clinical diagnosis	Pul. tbc. laryngeal tbc	Ext. active progressive pul. tbc	Active chr. pul. tbc	Mil. tbc	No record	No record	Advanced bi-lat. fib.-cas. pul. tbc with cavitation Tbc pharynx and larynx	Exten. bi-lat. chr. and acute progress. Tbc Tbc pharynx and larynx Tbc buccal mm.	Chr. bi-lat. fib. cas. pul. tbc Laryngeal tbc Lingual tbc	Tbc meningitis Miliary tbc
Autopsy findings	Not done	Chr. bi-lat. fib.-cas. Tbc with cavitation Tbc enteritis Miliary tbc Broncho-pneumonia	Chr. pul. tbc with cavitation Tbc trachea, buccal mucosa and right hip Tbc ulcer jejunum Tubercles in liver, spleen and kidney	Not done			Not done	Not done	Not done	Not done

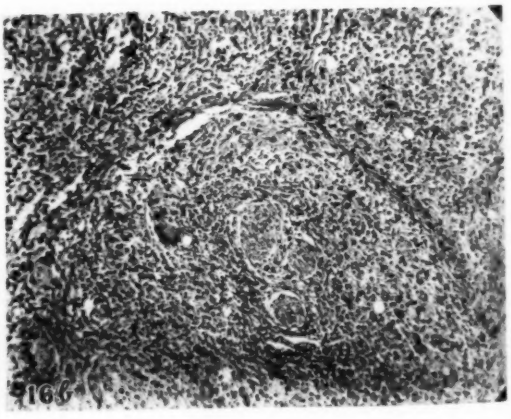
* Present at death.
† Up to death of patient.











Figs. 12–16b

and the other on the opposite side of the mouth, on the gingival margin, where an extraction previously had been made. Another was a palate case, no. 20, and the third, a tongue case, no. 21.

The case synopses follow.

13: N. Y. U. C. D., male, age 32. Slowly progressive, warty excrescent lesion of gingiva, involving first the lower 3rd molar, and gradually extending anteriorly about the 2nd molar, 1st molar and 2nd bicuspid, with subsequent loosening of teeth. The lesion also extended on to soft palate and uvula. Biopsy from gingiva showed tuberculosis. *Course:* Progressively worse. *Outcome:* Died 2½ years following recognition of oral lesion, with clinical diagnosis of pulmonary and laryngeal tuberculosis.

14: M. H., male, age 20. Developed 2 typical tuberculous ulcers of gums, one in the retromolar region (where no extraction was made), and the second on the opposite side where extraction previously had been made. No biopsy performed. *Course:* Progressive. *Outcome:* Died 5 weeks after observation of oral lesion. Autopsy diagnosis was chronic bilateral fibrocaseous tuberculosis with cavitation, tuberculous enteritis, amyloidosis, miliary tuberculosis, and bronchopneumonia.

15: M. H., male, age 25. Showed red nodular mulberry lesion of gingiva, extending to mucobuccal fold. Teeth in area loose. Biopsy showed tuberculosis. *Course:* Ambulatory. *Outcome:* Died 5 months after observation of oral lesion. Autopsy diagnosis of chronic pulmonary tuberculosis with cavitation, tuberculosis of trachea, buccal mucosa and right hip, tuberculous ulcer of jejunum, and tubercles in liver, spleen and kidney.

Case 21

Fig. 12. Photograph, showing tuberculous ulcer of tongue

Case 23

Fig. 13. Photomicrograph: tuberculous osteomyelitis

Case 24

Fig. 14. Photomicrograph: tuberculous lymphadenitis

Case 22

Fig. 15. Photograph of tuberculosis of mucous membrane, lower left side

Case 25

Fig. 16A. Photograph, showing lesion, upper left: hard palate. (Courtesy of Dr. L. V. Hayes, New York City.)

Fig. 16B. Photomicrograph (see text)

16: N. Y. U. C. D., male, age 46. Revealed extensive mouse-eaten ulcerative lesion involving gum and mucobuccal fold. Teeth in area loose. Lesion progressive. *Course:* Progressive. *Outcome:* Died 4½ months later, after observation of oral lesion (Bellevue Hospital). Diagnosis of "impression miliary tuberculosis." *Note* (Dr. James Alexander Miller)*:* "Small amount of sputum is evidence of blood-borne infection."

17: N. Y. U. C. D., female, age 32. Showed hypertrophic mulberry lesion of anterior buccal ridge. Biopsy showed tuberculosis. *Course:* Unknown. *Outcome:* Unknown.

18: N. Y. U. C. D., male, age 52. Showed deeply ulcerated ulcer on gum, first noticed when tooth was removed 5 months previously. Biopsy showed tuberculosis. *Course:* Unknown. *Outcome:* Unknown.

19: M. H., male, age 33. One week after admission rapidly developed ulcer in centre of soft palate, associated with laryngeal progress. No biopsy made. *Course:* Rapidly progressive. *Outcome:* Died 5 months after onset of oral lesion. Diagnosis of extensive bilateral fibrocaseous tuberculosis, and tuberculosis of pharynx and larynx.

20: N. Y. U. C. D., and M. H., male, age 36. Appeared at clinic for extraction. Showed extensive mulberry papillary eruption over entire soft palate extending back into throat. Smears from lesion showed tubercle bacilli. *Course:* Rapidly progressive. *Outcome:* Died 3 months after observation. Diagnosis of active pulmonary tuberculosis, and tuberculosis of pharynx and larynx.

21: B. H. and M. H., male, age 58. Patient admitted with dime-sized ulcer of right posterior border of tongue, with edges of roughened cusp of third molar in apposition to lesion with a history of 3 weeks' duration. Seven months later general condition and oral lesion slightly improved. Following this, lesion became progressively worse. *Course:* Progressively worse. *Outcome:* Died one year after observation of oral lesion. Diagnosis of chronic pulmonary tuberculosis, bilateral, fibrocaseous, and laryngeal and lingual tuberculosis.

22: N. Y. U. C. D., male, age 50. Showed extensive papillary ulceration with indurated border, involving gum and floor of mouth. Simulated carcinoma. Biopsy showed tuberculosis. Diagnosis of oral tuberculosis led to recognition of pulmonary involvement. *Course:* Progressively worse. *Outcome:* Died two months following observation of oral lesion. Diagnosis of tuberculous meningitis.

Case 13 is illustrative of this class, except that the lesion was less typical in mulberry appearance, and that the patient lived a considerably longer time than the others of this group.

The two palate cases, 19 and 20, are similar in that both represent rapid progressive lesions with fatal outcomes in short periods of time, and that both were associated with laryngeal tuberculosis. They differed in that case 20, when first seen by us, showed an extensive mulberry papillary eruption involving the entire soft palate, whereas case 19 (no biopsy) presented mainly a single ulcer, irregular, shallow in type, about $\frac{1}{2}$ by $\frac{1}{4}$ inch, that seemed to coincide with rapid development of the laryngeal lesion. Both of these cases, as is so often noted with extensive laryngeal involvement, manifested painful difficulties in taking food. These two cases, as well as cases 13 and 21, strongly suggest more than one method of spread of the tuberculous process.

Case 21, tuberculous ulcer of tongue, our single case of tuberculosis of the tongue, the lesion which receives the greatest concern in the literature, revealed a dime-sized oval ulcer on the tongue, located on the right posterior lateral and superior third. It is interesting to note that the lower right third molar, in lingual version, with a definitely roughened distolingual cusp, was found lying in the ulcer. Just how, directly or indirectly, this tooth influenced the production of the ulcer we do not know. When first seen by us this ulcer had been present only a short time. It is of further interest to note in this case that, three weeks after the patient complained of difficulty in swallowing on the right side, this ulcer developed. Also, in its ultimate course in this patient, the progressive involvement of the larynx on that side was much more marked than the progress of the ulcer of the tongue which showed some tendency to improvement, which may have been influenced by electrodesiccation.

Discussion

The cases in this group are not as strictly dental as those in the previous group, but nevertheless they do have dental application. Six of these 9 cases first appeared for dental consultation.

In summarizing the dental relationship in these 10 cases, looseness of tooth or teeth is the most impressive single finding. While the two palate cases showed no especial dental relationship, the lesion of the tongue showed a roughened cusp in apposition to the lesion, which is referred to previously.

In this group other factors worthy of comment are pain, looseness,

time of recognition in relation to pulmonary manifestation, relation to laryngeal involvement, and outcome.

Pain: The histories relative to pain or sensitivity were in keeping with the literature (6) (27) (30), seeming to correspond with the progress of the lesion. Pain and sensitiveness were more marked and troublesome in the palate and tongue cases.

Looseness: Our study of this group shows that a history or finding, indicative of looseness of one or more teeth, was prominent in most of the cases. In some the story of "tooth loose, wound failed to heal following extraction" recalls a similar story in carcinoma of the gums. In both groups the explanation is probably the same (46) (47) (48); the primary trouble is the disease not the tooth.

Time of recognition in relation to pulmonary manifestations: There is only one case (no. 22) in which we are sure that the recognition of the oral tuberculous lesion led to the detection of the pulmonary condition.

Relation to laryngeal involvement: Of these 10 cases, while on four we have no information as to laryngeal involvement, four of the remaining six were positive.

Outcome: The end-results in this group as to both patient and lesion are appalling. In two of the ten the outcome is unknown, but almost all the remaining 8 cases died rapidly: in 5 weeks, 3 months, 4½ months, 5 months, 7 months, 1 year, and 2½ years, respectively, all with their oral lesions (most of which progressed) present at death.

Class 3

Tuberculous osteomyelitis: A single case, no. 23, male, age 44, came to the dental clinic for dentures. He gave an indefinite history of trouble with his teeth, as a result of which all his teeth except four lowers had been removed. A biopsy specimen was taken from the upper right maxilla and the section showed a typical tuberculous osteomyelitis. While this case was lost track of, for 6½ years, recently we observed the patient again. He stated that he had been in excellent health during this time, being employed steadily as a painter, passing a physical examination every three years and having lost no weight, but being subject to a slight morning cough. Two and a half years following the biopsy specimen, he had his remaining lower four teeth removed by an outside dentist. At present, clinical and X-ray examinations of his mouth are negative, and physical examination of his chest shows few physical signs at the left base.

In our analysis of this interesting case there are two vital factors of which we can be certain. First, a section of bone from the patient's

mouth was typical, microscopically, of tuberculous osteomyelitis, and 6½ years later the fact that this individual has no physical complaints and has been able to continue his occupation and also raise a family (he has 6 children, the youngest 9 months of age) is paramount. The most natural question, "Does this patient have pulmonary tuberculosis?" cannot be answered with certainty. We do feel, however, that we are justified in comparing this case with the other groups, and, taking into consideration the type of lesion and behavior as well as one's knowledge of tuberculous osteomyelitis, we find that the case has also behaved as most cases of tuberculous osteomyelitis do. Whether the tuberculous osteomyelitis of the mouth was primary or secondary is not so much the question as the probability that, like other cases of bone tuberculosis, it was of blood-stream origin (and the prognosis of such cases of bone tuberculosis is correspondingly better).

Class 4

Tuberculous lymphadenitis: Only one case of our entire group fits into this category: case 24, a girl, 15 years of age, with a swelling of 6 weeks' duration located below the border of the mandible on the right side of the neck. She said that, two weeks after the swelling was first noticed, she had had a lower right second molar extracted with no relief to the swelling. For this swelling she was sent to the dental clinic. The mass had been incised 3½ weeks previously, and from this area caseous material was expressed. A biopsy taken from this area revealed typical tuberculosis in broken-down lymphoid tissue. No other history or evidence of tuberculosis was noted at that time. The girl was advised to report to her own physician. At present, 4½ years later, we have been informed that she received "light treatment" and also that she had had no illnesses since the previous lymph-node episode.

From a general medical standpoint this case is a typical illustration of most cases of tuberculous lymphadenitis:—the location in the neck in a young subject, eventually clearing up and no associated evidence of tuberculosis elsewhere. From the dental standpoint the removal of the tooth for this swelling and the referring of the patient to a dental clinic shows the lack of appreciation of the true nature of the condition in this case.

Class 5

We have now finished with those cases in which we feel that the diagnosis of tuberculosis is well established. This last group is presented

solely to illustrate difficulties in differential diagnosis, all four of them clinically having suggested carcinoma. The first three cases clinically, on account of their ulceration, extent and papillary formation, strongly suggested carcinoma, but all three microscopically showed pictures typical of tuberculosis. The last case was carcinoma.

The first case, no. 22 (previously presented under class 2), with an extensive papillary ulceration with indurated border located in the floor of the mouth and bicuspid region, died about 10 weeks later with a clinical diagnosis of tuberculous meningitis. The second case, no. 25, a colored woman, 30 years of age, with an extensive destructive lesion of the palate, showed a 3-plus blood Wassermann and no X-ray or clinical evidences of tuberculosis. Subsequently, she received antisyphilitic treatment and the lesion rapidly disappeared. Special tissue-stains for tubercle bacilli and *Treponema pallidum* were negative. Three months later clinical examination revealed no evidences of tuberculosis in this case. The third case, no. 26, female, aged 38, gave a 4-plus blood Wassermann. Her lesion was well defined and of an extensive ulcerative type and located on the posterior gum ridge, involving the mucobuccal fold. This patient also has received intensive antisyphilitic treatment with entire disappearance of her oral lesion; and, to date, 4½ years later, shows no clinical evidences of tuberculosis. The fourth case, no. 27, a male, age 52, appeared clinically as typical carcinoma of the lower posterior gum, but showed histologically a grade-II well-differentiated epidermoid carcinoma, in which some of the tissues presented a low-grade inflammatory reaction strongly suggestive of tuberculosis. Shortly after the biopsy was taken this patient was operated upon for carcinoma, and died almost immediately after operation. No autopsy was performed and we have no further information as to the correctness of the diagnosis of tuberculosis suggested by the biopsy.

(In fairness to Dr. Perla, it should be noted that all four cases of this group, in two of which the diagnosis is wrong, were diagnosed by one of us (C. G. D.) and not by Dr. Perla.)

When one considers difficulties in the diagnosis of lesions of such character, the triad of syphilis, carcinoma and tuberculosis must be considered. Very frequently attention has been called to this triad in extra-oral locations, while in respect to the mouth major attention has been given to the tongue.

In respect to such difficulties and the seriousness of such errors we

again call attention to that excellent article by Finney and Finney (32), who report 15 cases of tuberculosis of the tongue, 3 of which had been erroneously operated upon as carcinoma. Also, Rubin (27), previously referred to, cites one case of tuberculosis erroneously diagnosed as carcinoma and another case of carcinoma erroneously diagnosed as tuberculosis.

Combinations of two members of this triad may occur in the same individual at the same time, or less frequently in the same lesion, making their diagnosis more difficult and more imperative.

The frequent association of malignant tumor and syphilis in the mouth of the same individual has been emphasized by many observers, but it is outside the province of this study to refer to it further.

The association of tuberculosis and syphilis in the same individual is so frequent that it should be kept in mind in all cases in which differential diagnosis is necessary. The presence of a positive or negative Wassermann or Kahn test, while helpful, is not conclusive, and the histological features (of tuberculosis) are not absolute, as cases 25 and 26 show.

Whether there is an antagonistic effect between tuberculosis and carcinoma, as has been suggested (45) (49) (50), we do not know. Our experience with approximately 100 malignant tumors of the mouth suggests this antagonism.

SUMMARY

Twenty-seven cases showing oral lesions are reviewed, in 24 of which the diagnosis of tuberculosis is well founded.

Three of these cases are presented to show difficulties in diagnosis: one a case of carcinoma which showed a suspicious associated tuberculous reaction; and 2 cases which resembled tuberculosis histologically, but clinically were syphilitic.

The 24 cases of tuberculosis classified on a basis of pathogenesis showed: Class 1, 12 apex-socket cases; class 2, 10 oral mucous-membrane cases; class 3, one tuberculous osteomyelitis; and class 4, one tuberculous lymphadenitis.

An appreciation of the two following summary lists of the two major classes will add to our knowledge of their pathogenesis. The first relates to mortality, and the second is a comparison between classes 1 and 2.

DEATHS

Case number	*Time postoperative*	*Diagnosis*
		Class 1: apex-socket
1	2½ years	Chronic pulmonary tuberculosis.
2	1 month	Bilateral fibrocaseous tuberculosis with marked cavitation; diabetes mellitus.
8	3 weeks	Pneumonia; pulmonary tuberculosis.
9	11 months	*Autopsy:* Bilateral fibroulcerative pulmonary tuberculosis; tuberculous alveolar abscess; tuberculous jejunum; tuberculous adrenal (M.E.).
11	11 months	*Autopsy:* Chronic pulmonary tuberculosis with cavitation; tuberculous pneumonia; healed tuberculous spondylitis; kyphoscoliosis (neck organs not removed).
12	15 months	Chronic bilateral ulcerative tuberculosis.
		Class 2: mucous membrane
13	2½ years	Pulmonary tuberculosis; laryngeal tuberculosis.
14	5 weeks	*Autopsy:* Chronic bilateral fibrocaseous tuberculosis with cavitation; tuberculous enteritis; amyloidosis; miliary tuberculosis; bronchopneumonia.
15	5 months	*Autopsy:* Chronic pulmonary tuberculosis with cavitation; tuberculosis of trachea, buccal mucosa and right hip; tuberculous ulcer of jejunum; tubercles in liver, spleen and kidney.
16	4½ months	Miliary tuberculosis.
19	5 months	Extensive bilateral fibrocaseous tuberculosis; tuberculosis of pharynx and larynx.
20	3 months	Active pulmonary tuberculosis; tuberculosis of pharynx and larynx.
21	1 year	Chronic pulmonary tuberculosis, bilateral, fibrocaseous; laryngeal and lingual tuberculosis.
22	2 months	Tuberculous meningitis.

Comparison of classes 1 and 2

Subject heading	*Class 1: apex-socket*	*Class 2: Mucous membrane*
Number of cases	12	10
Outcome	6 dead: 6 living	8 dead: 2 no record
Location	8 apex: 4 socket	1 tongue, 2 palate, 7 gingiva
Dental evidence	X-ray	Looseness of teeth; mouse-eaten ulcer of mucous membrane; pain
Medical evidence:		
Length of pulmonary history	Relatively long	Very short
Laryngeal incidence	Low	High
Pathogenesis	Blood-stream	Blood-stream Direct lymphatic

CONCLUSIONS

We conclude, as a result of a fact-finding critical analysis of 27 cases with oral lesions, in twenty-four of which a diagnosis of tuberculosis is well founded, that:

1. Tuberculous lesions of the mouth may have dental application.
2. The lesions fall into two main groups, namely, those involving the apex or socket and those involving the mucous membrane.
3. The apex and socket cases, especially the former, are most frequently accompanied by bone destruction, radiographically, around the tooth root.
4. The mucous-membrane cases most frequently involve the gingiva, and present a mouse-eaten ulcerative appearance which is usually associated with looseness of the tooth.
5. Both occur secondary to advanced pulmonary tuberculosis.
6. In the apex and socket cases we feel that the tubercle bacilli reach the oral cavity by way of blood-stream.
7. In the mucous-membrane cases the infection is spread by direct and lymphatic extension, in addition to blood-stream transport.
8. In the mucous-membrane cases laryngeal involvement is frequently associated, and the prognosis is particularly grave.
9. The histological picture of tuberculosis is very characteristic, but may be simulated by syphilis.

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TUBERCULOSIS OF THE TONGUE

With a Report of 2 Cases[1,2]

RIGNEY D'AUNOY, EMMERICH VON HAAM AND JOHN CONNELL

Tuberculosis of the tongue is rare. Morgagni, in 1761, probably recognized the condition for the first time, describing tubercles on the tongue, but not clearly defining what he meant by the term "tubercle." Portal in 1804 reported the first authentic case. Louis in 1825, Fleming in 1850, Buzenet in 1858, Julliard in 1865, reported cases. Delavan in 1886 collected 47 cases; Wedenski in 1895 compiled 112 case reports; Scott in 1916 summarized 231 cases that had appeared in the literature; Carmody in 1915 tabulated 277 cases; Durante in 1917 stated that about 250 cases had been recorded up to October 20, 1916, and added five cases of his own. Morrow and Miller in 1924 collected 282 cases, of which 16 were their own; Bass in 1926 reported two additional cases and stated that less than 300 cases had been reported. Todd in 1926 reported three cases and tabulated a total of 311; Feldman the same year found a total of 283 cases reported, but stated that, in view of the difficulty of completely reviewing the literature on any subject, it was probable that the actual number of authentic cases reported was somewhat larger. D'Aunoy and Miller in 1929 reported three cases, and tabulated a total of 334 cases, 97 of which originated in the United States.

Autopsy observations also tend to support the relative infrequency of lingual tuberculosis. Willigk found two cases in 1,317 autopsies performed on tuberculous subjects; Fisher, six cases in 1,500; Chiari, 12 cases in 625; Fowler and Godlee, four in 382; and Adami and McCrae, no cases in 417 autopsies. Statistics of the Charity Hospital of Louisiana at New Orleans reveal the occurrence of three cases of lingual tuberculosis in 13,923 consecutive autopsies, approximately 15 per cent of which were on tuberculous subjects. Accordingly, there are only 27 cases of tuberculosis of the tongue reported in more than 6,000 autopsies

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on tuberculous subjects performed by different men in various parts of the world.

Feldman, in his excellent review, suggested that, were more attention given to the tongue in the course of physical examination and in the autopsy room, the relative rarity of lingual tuberculosis would be disproved. During the past six years, we have carefully searched for tuberculosis of the tongue on the wards and in the autopsy room of the Charity Hospital of Louisiana at New Orleans, and have observed two cases. These make a total of five cases seen at the Charity Hospital during the past 29 years in 730,524 admissions, of which 24,548 were for tuberculosis. We have further searched the literature since our report of 1929, and find 21 more cases (table 1). These, with the two cases here reported, bring the total number of cases of tuberculosis of the tongue recorded in medical literature to 357.

CASE REPORTS

1: E. S., white male, 81 years, suffered from pulmonary tuberculosis for three years. Autopsy (A-36-430) revealed chronic pulmonary tuberculosis, fibroid type, with bronchiectasis, cardiac hypertrophy, prostatic hyperplasia, and ulcer at base of the tongue, which, on microscopic examination shows typical tuberculosis (figure 1).

2: F. J., white male, 50 years, developed pleurisy with effusion eight years ago, since which time he stated that he had had a bad cough with much expectoration. Physical examination revealed bilateral pulmonary tuberculosis. Autopsy (A-36-387) showed chronic fibroid pulmonary tuberculosis with cavitation at both apices, tuberculous pleuritis, tuberculous laryngitis and glossitis. The tongue was indurated, especially along its right lateral border. Microscopically, it showed diffuse lymphocytic infiltration, with small typical tubercles scattered throughout the indurated margin (figure 2).

AGE, SEX AND RACIAL INCIDENCE

The largest number of cases of lingual tuberculosis has occurred after the fortieth year, with a slight preponderance between the fortieth and fiftieth years. The youngest patient on record, that of Sinibaldi, was five and a half years old. Fantozzi collected reports of four patients under 10 years of age. Two patients of Zintsmaster and Handfield-Jones were 80 years old. No cases are recorded in infancy, nor have any cases been described in the Negro. Males are more frequently affected than females, the ratio of males to females being 4:1, according to Wedenski,

5:1, according to Schliferowitsch, and 5.3:1, according to Scott. In the series we have collected, the ratio of males to females is 22:1. This disparity is indeed remarkable, and we are not able to accept fully the view so often expressed in the literature that it depends entirely on traumatic and occupational factors. While traumatism is at times an important predisposing factor in the production of lingual tuberculosis, and while probably the male is more liable to injury than the female and does engage in occupations, such as shoe-making and carpentry, which have

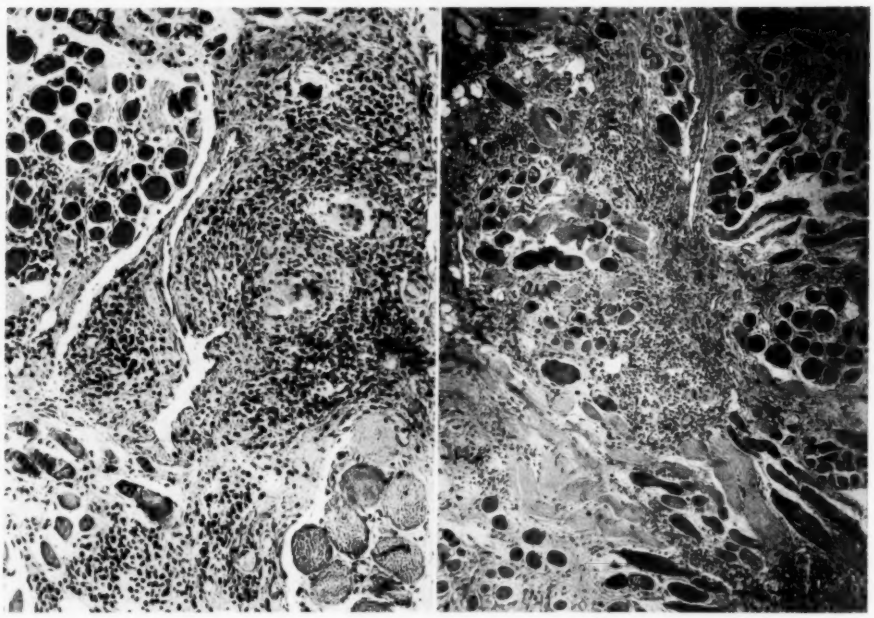

Fig. 1 Fig. 2

For description of figures see text

not as yet been generally invaded by the opposite sex, it is certainly more than suggestive to note that the case histories in lingual tuberculosis fail to show that many of the males affected were engaged in such occupations, or give with any frequency indications of traumatism to the tongue, or factors predisposing to its traumatism. Feldman's suggestion of sex susceptibility appears plausible and is an hypothesis that undoubtedly deserves most serious consideration in any attempt at explaining this remarkable sex disparity in the incidence of tuberculosis of the tongue.

AETIOLOGY AND MODES OF INFECTION

Tuberculosis of the tongue is naturally caused by the lodgment of tubercle bacilli in the tissue of the tongue and their subsequent proliferation. The routes of localization of invading bacilli must necessarily be considered from a purely theoretical standpoint. Infection by means of the blood-stream, by the lymphatics, by extension, or by actual contact are all admittedly possible, but in any case extremely difficult of ultimate proof. In this connection, there must also be considered the varying virulence of invading organisms and the local host-tissue resistance encountered. In the case of the tongue, this local resistance depends, in addition to general immunological laws, upon certain well-defined specially operating factors, such as vascularity, peculiar mucosal structure, constant movement of the organ, supposed germicidal action of glandular secretions, and the protective action of microbial antagonism. There can be no doubt that trauma, determining circumscribed areas of diminished tissue vitality or resistance, accounts for some contact or direct infections. Organisms so lodged, as can be readily proved, follow the same general biological activity noted by Cornet in his experiments with tubercle bacilli. However, that the independent occurrence of lingual tuberculosis to the complete exclusion of tuberculous processes or foci in other parts of the human organisms is frequent, is improbable. So-called primary tuberculosis of the tongue, even in spite of such cases as Clarke's and Schliferowitsch's, if occurring, is extremely rare. The lingual localization is usually secondary to a tuberculous process, either active or arrested, in other parts of the body.

PATHOLOGICAL LESIONS

Strictly speaking, cases of lingual tuberculosis do not present distinct or differing anatomicopathological types; they simply show diverse forms of the same process manifesting differing morphological aspects, depending on the virulence of the invading organism, the specific host resistance encountered, and the tissue elements primarily invaded. Still, such morphological differences have been made the basis for type differentiation by some; although the process, no matter what its final physical configuration may be, is always characterized by tubercle-formation, with the usual central caseation, the occurrence of so-called giant cells, connective-tissue proliferation with at times round-cell infiltration, and occasionally abscess-formation, all occurring either in the lingual parenchyma or in the dermis of the mucosa.

If the dermis of the mucosa is primarily affected, the lesion usually assumes some characteristics peculiar to cutaneous lupus. Thus, it is initially grayish, resistant to the touch, elevated, and rather discrete. Such lesions are spoken of clinically as *glossodermatitis tuberculo-fibrosa*. Should ulceration supervene, the lesion is then designated clinically as *glossodermatitis tuberculo-ulcerosa*. When the lingual parenchyma, as represented by the intramuscular connective tissue, is primarily invaded, the lesions tend to coalescence or dissemination, with much destructive ulceration. Such lesions are designated clinically as *confluent tuberculosis, nodular tuberculosis or granuloma tuberculare*. Each form may preserve its general morphological characteristics over a longer or shorter period. In general, it may be said that the so-called lupoid types are associated with or accompany a slow tuberculous process, usually of the lungs, while the ulcerative and necrotic lesions are generally concomitant with rapidly developing, destructive lesions of other organs. Danlos, Lévy-Franckel, Dainville and others recognized clinically a papillomatous or verrucose type, so designated when the papillae are markedly infiltrated by lymphoid elements. The ulcer is the physical form under which lingual tuberculosis most frequently manifests itself, the tip of the tongue being the site of election in the largest number of reported cases, with lesions of the border, dorsum and base occurring in the frequency mentioned.

CLINICAL MANIFESTATIONS

In the early stages of tuberculosis of the tongue there are no subjective disturbances. The initial lesion usually develops slowly and painlessly until ulceration ensues. Then, pain due to the passage of food or to attempts to move the tongue, as during phonation, is prominent. Ptyalism, the result of reflex secretory stimuli, is marked, and usually appears rather early. Regional adenopathy is generally present, developing, as a rule, early in the ulcerative type of lesion. In the lupoid types, adenopathy is either absent or present only late.

DIAGNOSIS

In the early stage of the disease, if diagnosis is limited to physical observations, it generally proves difficult. Confusion with malignant disease or with syphilis is the most common diagnostic error, made at times even in the presence of widespread tuberculous lesions in other parts of the body.

Histobiological and biological examinations of excised tissue are the only positive diagnostic criteria. Search should always be made for the specific microörganism, and for this purpose Gram's method, as well as Ziehl's, or one of its modifications, should be employed. Durante stresses the fact that both the margin and the fundus of ulcers should be searched for the typical histopathological lesion. This, in our experience, is most important. At times, much difficulty is encountered in differentiating tuberculosis from other granulomata, and it is in these cases that serological investigations and biological tests with portions of the excised material will prove diagnostically conclusive.

PROGNOSIS

Generally stated, the prognosis in lingual tuberculosis is unfavorable. This is especially so because the lesion is usually a manifestation of a bronchopulmonic or generalized tuberculous process. If the lesion is single or so-called primary, by which is meant essentially a lesion in an organism in which other tuberculous foci or processes are not distinctly discernible or arrested, the prognosis may be considered fair. Von Ruck, White and Marcy, however, state that even in fairly advanced cases the prognosis is rather favorable with tuberculin therapy. Lactic acid, as topical applications, has been used, especially by Continental physicians.

SUMMARY

1. According to reports occurring in medical literature, lingual tuberculosis is infrequent, only 357 cases being recorded up to January, 1936.

2. It is usually associated with tuberculosis in other parts of the body, generally the lungs.

3. It is improbable that primary tuberculosis of the tongue in the broadest acceptance of the term is of frequent occurrence, although readily induced experimentally.

4. Diagnosis can be accomplished with certainty only by the use of histobiological methods.

5. Treatment is unsatisfactory and the prognosis unfavorable.

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TABLE 1

AUTHOR	YEAR	AGE	SEX	PHYSICAL ASPECTS OF LESIONS	LOCATION OF LESIONS	ACCOMPANYING ADENOPATHY	EVIDENCE OF TUBERCULOSIS FOUND IN OTHER ORGANS OR SYSTEMS	ACID-FAST BACILLI FOUND IN			HISTOLOGICAL EXAMINATION
								Sputum	Scrapings	Tissue	
		years									
Rudoy	1927	22	M	Ulcer	Tip		Lungs, larynx				
		30	M	Ulcer	Superior surface		Pulmonary	Yes			
		54	M	Ulcer	Inferior surface		Pulmonary	Yes	Yes		
Valtan	1929	40	M	Ulcer	Margin, dorsum		Bilateral pulmonary		Yes		
Nicolas	1930	61	M	Ulcer	Left margin		Bilateral pulmonary	No	No	No	No
Vigne and Montcerisier	1930	25	M	Ulcer	Inferior surface		Died of tuberculous meningitis	Yes			Tuberculosis
Du Bois	1931	64	M	Ulcer	Tip				Yes		
Nodoff	1931	46	M	Ulcer	Tip	Yes		No	No	No	Tuberculosis
		43	M	Ulcer	Inferior surface		Bilateral pulmonary	Yes			Tuberculosis
Melnikoff	1931	55	M	Ulcer	Tip		Pulmonary, two years	Yes			Tuberculosis
Oudard, Coureaud and Bideau	1931	39	M	Ulcer							Tuberculosis
Mattice	1932	39	M	Ulcer	Tip		Pulmonary	Yes	Yes		Tuberculosis
Imperiale	1932	42	M		Tip			No	No	No	Tuberculosis
Giordano	1932	35	M	Ulcer	Margin			No	No	No	Tuberculosis
Duany and Figueras	1932	50	M	Tumor	Tip	No	Infiltration of both lungs	No	No	No	Tuberculosis
Lemaitre, Nuytten and Bedrine	1933	56	M	Ulcer	Margin	None	X-ray evidence of pulmonary tuberculosis				Tuberculosis
Becco	1933	38	M	Ulcer	Tip		Bilateral pulmonary	No	No	No	Tuberculosis
Schneidewind, d'Amato and Latienda	1934	45	M	Ulcer	Tip	Yes	Infiltration of both lungs	Yes			Tuberculosis
Linka Giovanni	1935	50	F	Ulcer	Tip	No	No	Yes			Tuberculosis
Rousseau-Decelle, Lattēs and Merle-Béral	1935	40	M	Ulcer	Anterior surface	Yes				No	Tuberculosis
Marin	1935	59	M	Ulcer	Anterior aspect		Bilateral pulmonary	Yes		Yes	Tuberculosis
D'Aunoy, von Haam and Connell	1936	81	M	Ulcer	Base	No	Pulmonary	Yes			Tuberculosis
D'Aunoy, von Haam and Connell	1936	50	M	Tumor	Margin	No	Pulmonary	Yes			Tuberculosis

OESOPHAGOPLEURAL FISTULA IN A CASE OF TUBERCULOUS PYOPNEUMOTHORAX[1]

A. J. KANTER AND IRVING MADOFF

Oesophagopleural fistula is encountered infrequently. There are, no doubt, many unreported cases, since the condition may be either diagnosed incorrectly or remain undiagnosed. Cases of sudden perforation with rapid death often give symptoms of acute abdominal disease, as, for example, those reported by Christie and Petrén, laparotomy having been performed in both instances for ruptured peptic ulcer. In many instances, therefore, the diagnosis is made only at autopsy.

Perhaps the earliest reported case is that of Booerhaave (2) in 1767, in which, postmortem, a transverse rupture of the lower oesophagus with communication into both pleural cavities was found. The communication apparently occurred spontaneously, although Fitz (1) doubts whether the rupture occurred antemortem. Among other early reports are those of Dryden (2) (1788), Guersent (2) (1812), Bouillard (2) (1823), Meyer (2) (1858), Grammatzki (3) (1867), Charles (4) (1870) and Osler (5) (1898). Excellent reviews of the subject have been given by Fitz (1), Smead (6), Ballin and Saltzstein (7) and D'Istria (8).

The aetiological factors and exact modes of formation of the abnormal communication are difficult to determine from many of the case reports. In some, the evidence of a definite aetiological diagnosis is so doubtful as to make a classification almost impossible. The majority of the cases, however, may be included under the following general aetiological headings:

1: Trauma: This may occur from within, as in the case of foreign-body ingestion (Sandahl (9), Ginsburg (10)), or during exploration and dilatation of the oesophagus by sounds, bougies, etc. (King (11), (12), Myerson (13), Friedenwald and Morrison (14)); or from without, as a result of a crushing injury to the chest (Esser (15), Raimondi (16), Thöle (16), Whipham (16), Murdoch (17)). A very unusual case is reported by Petrén (16) in which the interior of the oesophagus was subjected to

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seven atmospheres of air-pressure with rupture into the left pleural cavity. Vinson (18) reports a case of perforation due to an unusual type of trauma.

2: Spontaneous rupture: Included under this category are cases in which rupture of the oesophagus into the pleural cavity occurs without any demonstrable evidence of previous local disease. The main factors here concerned seem to be weakness of the oesophageal wall, together with the production of increased pressure within the oesophagus, as by vomiting. Death is usually sudden, or it occurs within a short time and the diagnosis may be made only at autopsy. Williams and Boyd (19) report a case with a definite history of alcoholism, which may have caused some weakening of the oesophageal wall. Vomiting may be due to volvulus of the intestine (Lewis and Smead (6), Sheldon (20)), gastro-intestinal upset (Menne and Moore (21), Raestrup (22)), purgation (Bowles and Turner (23)), meningitis (Gott (24)). An increase in pressure within the oesophagus might also conceivably be due to straining (Griffith (25)).

3: Carcinoma of the oesophagus: A rather infrequent complication of cancer of the oesophagus is oesophagopleural fistula. Such cases have been reported by Friedenwald and Morrison (14), Bonnamour and Giraud (26), Surmount and Maire (27), and a few others.

4: Diverticulum of oesophagus: Sigora (28) gives an excellent discussion on the subject of traction and pulsion diverticula, and reports a case in which oesophagopleural fistula resulted from perforation of a diverticulum. Woolley (29) reports a case of rupture of an oesophageal diverticulum following intestinal obstruction.

5: Empyema (simple): As an occasional cause of fistula between the oesophagus and pleura, empyema due to pyogenic organisms is encountered. Such cases have been reported by Vos (30), Wall (31), Ballin and Saltzstein (7), McCormick (32), Arquellada (33), Acuna and Bettinotti (34), Hand and Lee (35). Recovery is often the outcome in such cases.

6: Simple ulcer: Christie (36), Petrén (37), Miller (38) and Roszak (39) report cases in which perforation of the oesophagus into the pleural cavity is apparently due to the presence of an acute or chronic ulcer. The cases reported by Miller and Christie give a definite history of alcoholism.

7: Syphilis: Fonte (40) reports a case of oesophagopleural fistula of probable syphilitic aetiology on the basis of a syphilitic history. No proved cases were found.

8: Tuberculosis: Aside from our report, we have found only one instance of oesophagopleural fistula in a case of tuberculosis. In this case, reported by Martens (41), empyema developed in the course of chronic pulmonary tuberculosis. Several years following two thoracotomies for drainage of the empyema, many bronchopleural as well as oesophagopleural fistulae had formed and could be seen through the chest wound. The case was not subsequently followed.

Case Report

N. F., white male, age 45, cabinet-maker, was admitted to Montefiore Hospital, February 11, 1933, with history of chronic pulmonary tuberculosis since spring of 1930. Examination on admission revealed far-advanced bilateral pulmonary tuberculosis, with cavitation in right upper lobe. Sputum positive; but at his own request patient left hospital, September, 1933, slightly improved. While in hospital, was given symptomatic treatment, course was afebrile and patient was ambulant. In July, 1934, ten months after discharge, a febrile period occurred, and patient was admitted to another hospital, where fluid was removed from right pleural cavity, with air replacement on seven occasions. In August, 1934, he was readmitted to Montefiore Hospital. Examination now revealed pneumothorax on right side, collapsing the middle and lower lobes completely. The upper lobe was adherent at the apex and contained a fairly large cavity. There was a moderate amount of pleural fluid on the right. The left lung was unchanged. The larynx was negative. There had been loss in weight of 8 lbs. since September, 1933. The patient's condition otherwise was unchanged. The Wassermann and Kahn tests were negative. Repeated aspiration of chest fluid from August 27, 1934, to November 30, 1934, yielded sterile tuberculous pus. Subsequent taps revealed secondarily infected empyema fluid. The treatment was symptomatic, and fluid was removed from the right pleural cavity without air replacement for the relief of the dyspnoea. The temperature ranged irregularly between 97° and 101°F., and the patient's course was progressively downhill. In November, 1934, he developed a transient thrombophlebitis in both antecubital regions, which disappeared within two weeks. In December, 1934, a bronchopleural fistula was suspected, but methylene-blue injected into the right pleural cavity was not detected in the sputum.

Because of the purulent nature of the fluid and the apparently inadequate drainage afforded by tapping, a thoracotomy was performed on December 21, 1934 in the right posterior axillary line, 8th interspace, and closed drainage was instituted. Approximately 500 cc. of purulent fluid was drained daily until January 26, 1935, when the amount suddenly increased to 1,500 cc. The patient stated that some of the material which had come out of the

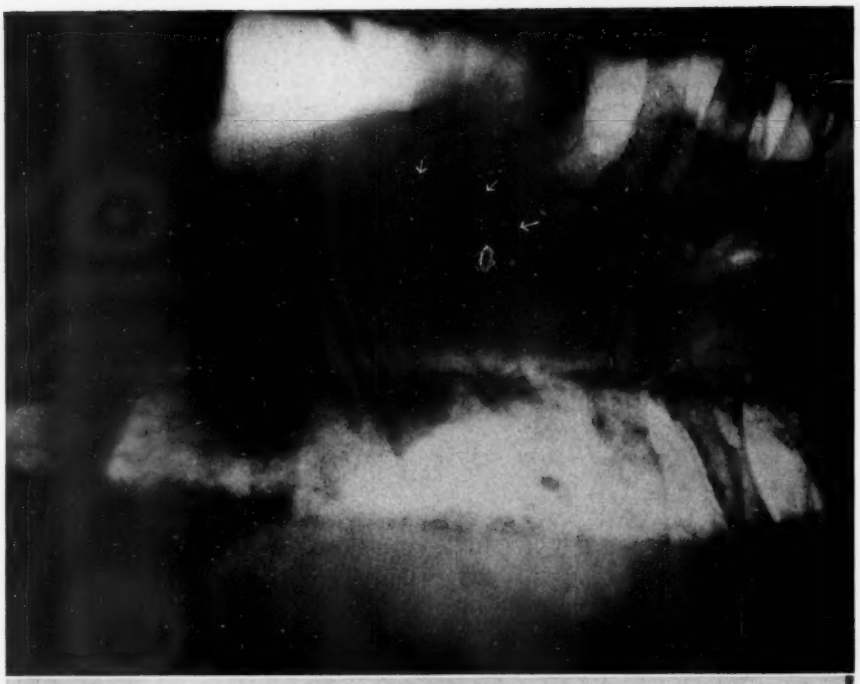

Fig. 1

Fig. 2

Figs. 1 & 2. Anterior and lateral views, showing a barium meal passing through the oesophagus and out into the fistulous tract (arrows)

thoracotomy tube that day had resembled food he had eaten (chocolate). Aside from this he had noted no change in his symptoms. Fluoroscopy during

Fig. 3. Posterior view of the oesophagus and right lung, with a probe passing through the fistulous tract into the pleural cavity

the ingestion of barium revealed the oesophagus outlined by barium, as it pursued an approximately normal course to the stomach. At a level just below the bifurcation of the trachea, however, a thin stream of barium was

seen to pass from the oesophagus apparently directly through the posterior mediastinum into the right pleural cavity just above the upper level of the effusion (figures 1 & 2). Oesophagoscopy was not performed because of the critical condition of the patient. In spite of continuous supportive rectal and subcutaneous clyses of glucose and isotonic saline, the patient became markedly emaciated and dehydrated, and died, February 6, 1935, the temperature dropping to 95° on the day of death.

Autopsy

Male, fairly well developed, but emaciated. Between 8th and 9th ribs in right posterior axillary line is an opening leading into pleural cavity, draining a mixture of greenish purulent material and food particles, especially when the body is in the recumbent position. *Thorax:* Right lung almost completely collapsed, occupying about one-fifth of total volume of pleural cavity at apex. Pleura thickened, and lined by granular necrotic layer of purulent material, and contains about 300 cc. of the mixture mentioned above. Lateral opening present in posterior mediastinum at approximately level of bifurcation of trachea, through which food particles can be expressed by pressure on mediastinum. Lung densely adherent to chest-wall and mediastinum, and contains in upper portion a cavity the size of silver dollar lined by caseous material. Below and lateral to this, is a second cavity of similar size with smooth wall. Remainder of right lung contains scattered areas of anthracosis, caseation and fibrosis throughout. Left lung voluminous, moderately firm, covered by thickened visceral pleura, and contains millet-sized grayish-yellow tubercles throughout. Also numerous anthracotic markings throughout lung, and soft enlarged anthracotic lymph nodes at hilum. Oesophagus normal throughout except at middle third, where there is an opening on right side posteriorly (figure 3). This leads into a tract about 1 inch in length, lined by ulcerated and partially epithelialized wall, which passes through posterior mediastinum to opening in right pleural cavity mentioned above. Epicardium shaggy, due to fibrinous pericarditis, and contains single bean-sized nodule of caseous material. Otherwise, heart not remarkable. Right lobe of liver bound by adhesions from its lower pole to lesser curvature of stomach and to hepatic flexure of colon. Stomach presents several ulcerations in antrum. Papillary mass in hepatic flexure of colon, and scattered caseous nodules throughout mesentery of jejunum and ileum. Remainder of gastroenteric tract negative. Spleen and kidneys contain many small yellowish tubercles scattered throughout.

Microscopical Notes

Fistulous tract: In the first portion of the tract is a small area of typical squamous-cell oesophageal epithelium with underlying musculature. Beyond this point epithelium is absent and is replaced by a slightly ulcerated surface.

Beneath it is granulation tissue, composed of lymphocytes, fibroblasts and epithelioid cells and some congested vessels. The submucosa is thickened by increased connective tissue. Beneath it, is a continuation of muscle layers typical of the oesophagus, containing several tubercles with central caseation and giant cells surrounded by epithelioid and round cells. Beyond the area of superficial ulceration, the lining of the tract is fairly smooth and consists mainly of fibrous tissue and some epithelioid cells. There is still underlying musculature, beneath which are a few small lymph nodes showing anthracosis, brownish pigmentation and tubercle-formation. Approaching the pleural end of the tract, the surface is again ulcerated by tuberculous caseation, and in this region there is no further musculature. At the lateral end there is a small portion of lung beneath the tract, showing anthracosis, atelectasis, fibrosis and some caseous tubercles. *Colon:* A section through the papillary mass reveals a typical tuberculous granuloma.

COMMENT

In view of the pathological findings, the probable cause of the oesophageal perforation was an extension of the tuberculosis from the previously involved and adherent mediastinum and pleura into the oesophagus. The process apparently consisted of tubercle-formation with subsequent caseation, which, with some change in the intraoesophageal tension, caused an extrusion of the caseous material into the pleural space; and a fistulous tract developed.

SUMMARY

An instance of an oesophagopleural fistula in a case of a chronic tuberculous empyema is reported, the aetiology probably being an extension of the tuberculous process into the oesophagus.

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TUBERCULOUS ENTEROCOLITIS

1. A Study of the Terminal Ileum and Colon by Barium Meal and Barium Enema[1]

N. I. FOX, C. H. WARFIELD AND L. O. LEADER

Tuberculous enterocolitis is very common in advanced stages of pulmonary tuberculosis. This has been shown in autopsy findings by S. G. Gant and by Goldberg, Sweany and Brown, who found intestinal ulcerations in about 80 per cent of the far-advanced cases of pulmonary phthisis. In the moderately advanced and minimal cases this percentage tapers off. However, the ulcerations in the bowel are frequent enough even in these stages of pulmonary tuberculosis, and they often contribute in no small measure to the further progression of the disease in the lungs. But, although we suspect its presence, clinically intestinal tuberculosis is not easily diagnosed. Abdominal pain, diarrhoea, local rigidity and tenderness over the caecum, or tumor palpable in the same region, are diagnostic of intestinal ulceration in far-advanced cases of pulmonary tuberculosis; but these symptoms are not common, or even rare, diarrhoea having occurred in only four of our 100 cases.

The vague symptoms, such as anorexia, nausea, constipation, and varying distress after meals are more common, but in themselves are insufficient for a diagnosis. The difficulty becomes still greater when one realizes that the degree of intestinal involvement does not always correspond to the amount of pulmonary involvement. Not infrequently, one sees cases with pronounced intestinal symptoms, such as abdominal pain and diarrhoea, in which the pulmonary findings are minimal and in doubt, and the diagnosis is missed until a later date when tuberculosis in the lungs becomes quite evident. One such case was treated as amoebic dysentery for months, before finally tuberculosis of the lungs was diagnosed and the patient was sent to a tuberculosis hospital.

Laboratory help in these cases is insufficient. The finding of tubercle bacilli in the stool, tuberculin reactions and blood studies are of little value in diagnosing intestinal tuberculosis. In this field, as in other fields of diagnosis, X-ray studies have been shedding considerable light, and as an objective study hold out the most promising possibilities.

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In 1911, Stierlin called attention to certain filling defects in the caecum and ascending colon in a barium-filled colon, which was proved at operation to be infiltrating and ulcerative intestinal tuberculosis. Later, these findings were substantiated by Case, by Schwarz, Gottwald and Novascinsky, by Faulhaber, by Lemon and by others, who have reported a number of cases with the Stierlin caecum filling defect on X-ray proved by surgery.

However, the subject received its greatest impetus when Brown and Sampson published their method of X-ray studies and findings in intestinal tuberculosis in the Trudeau Sanatorium in 1919 and 1920, and subsequently in their monograph in 1931. This brilliant work drew the attention of roentgenologists in this country and abroad, and a great deal of work on intestinal tuberculosis resulted.

Further extensive studies on the subject were reported by Cherry, by Granet and by Gershon-Cohen, the latter using the double contrast enema. To date, however, there is a wide gap between the positive diagnosis of intestinal tuberculosis with the X-ray and the percentage established by autopsy findings. Study of our rich material of moderately and far-advanced cases at the Cook County Hospital offers a good field for further investigation, with the hope that eventually the X-ray findings will equal those at autopsy.

Technique: The technique employed in this study was as follows: Barium sulphate, in the form of a standard prepared meal, was given seven hours before the first observation, the time after the ingested barium had reached the terminal ileum and in many cases had entered the caecum; so that we feel that seven hours is soon enough for the first observation. We also found it advisable to make another examination again in nine hours, since information not obtained at the seven-hour period could be found at the nine-hour period. Films were taken of the ileocaecal region at both observations.

A barium enema was used in this group of cases, using the standard technique. However, we feel that the colon should not be completely distended, since overdistention of the caecum may obscure the caecal findings. The injection of air into the colon was not attempted in this series.

Roentgen findings: The oral method, in our opinion, is the best for studying the ulcerative type of caecal tuberculosis. However, an examination of this region by X-ray is not complete unless barium is given

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 1. Observation of barium by mouth at 7 hours. Note the barium still remaining in the ileum, absence of barium in caecum and ascending colon, partially filled transverse colon and marked motility of the colon.

Fig. 2. Observation of barium by mouth at 9 hours. Same patient as fig. 1. Essentially the same findings, except that the irritability of the transverse colon is more marked and the ileal stasis at this hour is marked.

Fig. 3. Observation of barium by mouth at 9 hours, showing the marked irritability of the caecum and ascending colon and constriction of the terminal ileum. Note the demarcation of the pathological process in the proximal transverse colon.

Fig. 4. Same patient as fig. 3 except that the colon and ileum were filled by enema. Note the irritability of the caecum and narrowing of the ileum. The extent of the lesion is not as well shown as in fig. 3 when barium was given by mouth.

Fig. 5

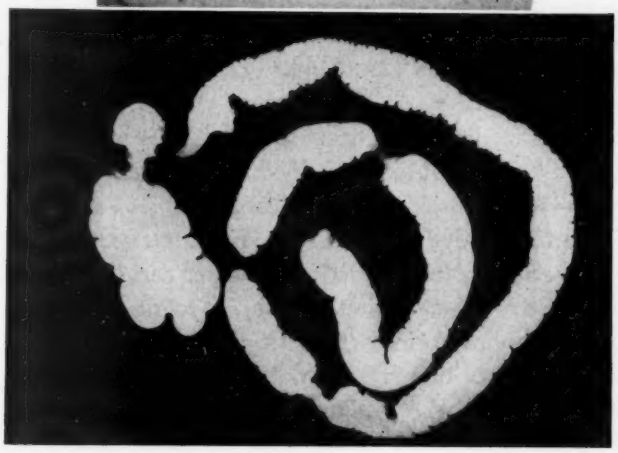

Fig. 6

Fig. 5. Barium by enema. Note the constriction of the terminal ileum and the linear effect, parallel to the long axis of the bowel and apparently due to destruction of the villi and not ulcer craters.

Fig. 6. Injection of barium in a resected specimen of the caecum and lower ileum. Note marked constriction of the terminal ileum and caecum at the ileocaecal valve; also three other constricted areas of the ileum. The soft-tissue mass of the terminal ileum is well seen. This represents the hyperplastic type of tuberculosis.

by mouth and by enema. The findings and signs of tuberculosis of the caecum coincide with those reported by other authors. The caecum and ascending colon were very irritable in the positive cases; that is, they failed to concentrate the barium and hold it. In order to evaluate this irritability, barium must be present in the terminal ileum as well as the colon distal to the pathological process, and only traces in the involved area. If at the first observation barium is seen only in the colon distal to the suspected area, then opinion as to the condition of the caecum is valueless, since barium must be feeding into this area in order for the observer to make a positive statement. Diminution of the calibre of the terminal ileum should be carefully noted, as well as stasis. In some of our cases the terminal ileum showed a linear effect, that is, striations were seen parallel to the long axis of the tube instead of the usual transverse ulcers. A study of the terminal three or four inches of the normal ileum, confirms the above statements.

The first group of cases studied consisted of 108 patients taken in order. There was no attempt at selection. The only requirements were a positive diagnosis of pulmonary tuberculosis and a physical condition, not necessarily ambulant or semiambulant, but such that it was felt that no harm would be done to any patient. Obviously, no severely toxic patient was examined. The majority belonged to the far-advanced group.

Eight cases were discarded because the plates were unsatisfactory. This left 100 cases distributed as follows: Sex, females, 92 and males 8; race, Negroes 47, whites 45 and Mexican 8; age, 13 to 65 years. The high incidence of females is due to the fact that we have a Women's Service. The males were included from other services merely to make an even hundred. In this first group, a roentgenological study of motility and of abnormalities, irritability and defects was made.

Table 1 summarizes our studies on motility, as determined by the position of the head of the barium column at seven- and at nine-hour intervals.

The terminal ileum was visualized in 97 cases at 7 hours and in 61 cases at 9 hours. It can be seen, by reference to table 1, that the ileum was visualized in practically all cases at 7 hours, but that the percentage with a visualized ileum at 9 hours was definitely higher in the pathological group.

We do not feel justified at this time to draw any conclusions from these figures, but hope at a later date to study this problem. Nevertheless, it is our impression that the ileum empties more slowly and that the

TABLE 1

HEAD OF COLUMN	NEGATIVE X-RAY				POSITIVE X-RAY			
	7-hour		9-hour		7-hour		9-hour	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Ileum	2	3.2	0		2	5.3		
Caecum	2	3.2	0		5	13.1		
Ascending colon	6	9.7	5	9.2	3	7.9	5	13.5
Transverse colon	15	24.2	13	24.0	7	18.4	6	16.2
Descending colon	27	43.5	25	46.2	11	28.9	11	29.7
Sigmoid	4	6.4	5	9.2	3	7.9	3	8.1
Rectum	6	9.7	6	11.1	7	18.4	12	32.4
Totals	62		54		38		37	
Visualized ileum	59	95.2	31	57.4	38	100.0	30	81.1

(The differences in the number of cases at the 7- and 9-hour intervals are due either to unsatisfactory films or to the fact that some of the plates were unavailable for other reasons.)

barium very rapidly traverses the affected portions of the bowel in the positive cases.

Of this group 38 were found to have abnormalities after the oral administration of barium. Tables 2, 3 and 4 summarize our findings as to the type of abnormality found, its location, and its relative frequency.

TABLE 2

SITE OF LESION	IRRITABLE	DEFECT
Ileum		4
Caecum	9	7
Ascending colon		2
Transverse colon		
Descending colon		
Caecum and ascending colon	1	4
Caecum, ascending and transverse colon	1	1
Caecum, ascending, transverse and descending colon	1	1
Ascending colon and ileum		1
Ascending, transverse and descending colon	1	
Caecum and ileum	1	1

In addition to the above, the following combinations of lesions were noted: The ileum was irritable and defective in one case; the transverse and descending colons were irritable and the ileum was irritable and defective in one case; and the caecum, ascending colon and transverse colon were defective and irritable, and the ileum was defective in one case.

Table 3 has been prepared in order to show the relative frequency with which the ileum and the various segments of the colon are attacked. Our results, as can be readily seen, agree with the work of most investigators on this point. The sites of the disease in the order of their frequencies were caecum 71 per cent, ascending colon 26.3 per cent, transverse colon 18.4 per cent and descending colon 10.5 per cent.

TABLE 3

SITE OF DISEASE	ALONE	COMBINED	TOTAL	PER CENT
Caecum	16	11	27	71
Ascending colon	2	12	14	36.8
Transverse colon		7	7	18.4
Descending colon		4	4	10.5
Ileum	4	6	10	26.3

In this group of 100 cases there were 48 with one or more cavities, 68 had positive sputum, 9 had tuberculous laryngitis, and only 4 presented intestinal symptoms. A comparison of their occurrence in cases in which the X-ray showed signs of tuberculous disease of the intestines and in those with negative X-rays appears in table 4.

TABLE 4

	TOTAL	POSITIVE X-RAY	NEGATIVE X-RAY
Cavity	48	26–54%	22–46%
Positive sputum	68	32–47%	36–53%
Tuberculous laryngitis	9	3–33%	6–67%
Intestinal symptoms	4	3–75%	1–25%

It may be noted from the above figures that the incidence of cavitation and positive sputum was almost equal in the two groups. These figures emphasize the high incidence of roentgenologically demonstrable enterocolitic lesions in cases with cavitation and positive sputum. The difference in the laryngeal cases is rather surprising, as one would expect a higher incidence in those with tuberculous enteritis, but this is perhaps due to the small number of cases.

A preponderance of intestinal symptoms (diarrhoea, abdominal pain, etc.), among those with roentgenological evidence of a specific enteritis is to be expected. The case with symptoms and negative X-rays may

perhaps belong to the group of so-called toxic diarrhoea, in which no organic lesions of the intestines are found at autopsy. This case is particularly interesting, as it was of a young colored woman who shortly after delivery broke down with a pneumonic form of tuberculosis, in spite of which she was getting along very well. The diarrhoea and abdominal pain responded promptly to intravenous calcium chloride when other measures failed. The patient was discharged about 18 months later in good condition.

In table 5 the presence of cavitation, positive sputum, tuberculous laryngitis, and intestinal symptoms in the 38 cases with positive X-rays is compared with the incidence of similar conditions in the 62 negative cases.

TABLE 5

X-RAYS OF BOWEL	TOTAL	CAVITY	POSITIVE SPUTUM	TUBERCULOUS LARYNGITIS	INTESTINAL SYMPTOMS
Positive	38	26–68.4%	32–84.2%	3–7.9%	3–7.9%
Negative	62	22–35.5%	36–58 %	6–9.7%	1–1.6%

There was one case of miliary tuberculosis, two of tuberculous peritonitis, one of tuberculous kidney, one of tuberculous meningitis, and two of bone tuberculosis among the 62 giving negative X-rays of the bowel. There were no such complications among the 38 with roentgenological signs of intestinal disease. It may be noted by comparing tables 4 and 5 that, among those with cavitation and those with positive sputum, only approximately one-half gave positive X-rays, but cavitation and positive sputum were far more common in those cases with X-ray findings of intestinal disease.

Table 6 deals with the relation of race to the incidence of positive X-ray findings in our series. As to race there is only a slight difference between the colored and the white, but a markedly higher incidence in the Mexicans. This latter is probably due to the more extensive and severe tuberculosis found in our Mexican patients.

TABLE 6

	FEMALES	MALES	COLORED	WHITE	MEXICAN
Total	92	8	47	45	8
Positive X-rays	36–39.1%	2–25%	15–32%	17–38.6%	6–75%

Our second series of cases consisted of 67 of the above 100. Again there was no attempt at selection. We took those that were available. After all, the population of the Cook County Tuberculosis Hospital is not static. Some die, some are sent to other institutions, and some are discharged. In addition, some patients could not coöperate in the administration of a barium enema. An ordinary barium enema, after the usual preparation, was given in the usual manner.

Of the 67, 58 were negative while 9 were positive, and showed the following: Caecum, irritable, 4; caecum, defective, 4; and ileum, defective, 1. In these positive cases the oral method was also positive, but by the latter method the changes were generally more marked than in the corresponding enema. In 12 of the cases which were positive by the oral method, no plate following an enema is available. A comparison reveals that of 26 positive orals, there were but 9 positive enemas, a ratio of almost 3 to 1. It is our opinion that a barium enema as well as a contrast enema should be used in conjunction with the barium meal. This high ratio may be due to overdistention of the colon, obscuring many of the findings.

SUMMARY

1. One hundred consecutive cases of pulmonary tuberculosis have been studied.

2. One hundred have been given barium meals; 67 have also been given barium enemas.

3. Forty-eight with cavitation showed an incidence of 54 per cent positive roentgen findings.

4. Sixty-eight with positive sputum showed an incidence of 47 per cent positive roentgen findings.

5. The incidence of cavitation (68.4 per cent) and positive sputum (84.2 per cent) in the cases with positive roentgenological findings is markedly higher than the corresponding figures (35.5 and 58 per cent) in those with negative findings.

6. The incidence of clinical findings is low, only 4 cases having symptoms, of which 3 were roentgenologically positive.

7. In our experience the incidence of positive findings is definitely higher by the oral method than by the barium enema.

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PRACTICAL APPLICATIONS OF CONTEMPORARY RESEARCH ON X-RAY APPARATUS AND TECHNIQUE FOR THE CHEST[1,2]

F. MAURICE McPHEDRAN, CHARLES WEYL AND S. REID WARREN, JR.

It has become increasingly evident during the past two years that those members of the American Sanatorium Association and the National Tuberculosis Association who are interested in the development of the technique of chest roentgenography may be divided into two groups:

1: A small number of roentgenologists who, by careful study or pertinent experience, have acquired a knowledge of the fundamental physical phenomena underlying chest roentgenography.
2: A large number of roentgenologists and sanatorium directors who, because they are forced to devote their time chiefly to clinical and administrative problems, have been unable to apply the results of recent roentgenographic research to their own laboratories. These results have often been described in papers and monographs written in technical phraseology unfamiliar to them.

The roentgenologists of group 1 have contributed invaluable experimental data and suggestions for research. They have enabled the engineers, who are concerned with investigations of apparatus and technique, to plan their work in such a way that the results may be ultimately applicable to the improvement and standardization of clinical roentgenography. This objective requires that the general plan of research be divided into two parts:

1: The solution by scientifically controlled tests of problems to which the physical phenomena of chest roentgenography give rise in order to obtain standards by which both the choice and the use of apparatus may be determined for optimum results.
2: The study of existing roentgenographic installations with a view to recom-

[1] Presented at a session of the Pathological Section at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

[2] The conclusions presented in this paper are based upon work at the University of Pennsylvania, conducted under grants from the National Tuberculosis Association.

mending methods for improving results and for minimizing the net cost of X-ray service without sacrificing the roentgenographic quality.

The roentgenologists and sanatorium directors described in group 2 above desire and need practical assistance in this important field. They require suggestions for economically modifying their apparatus and technique in accordance with modern standards. These suggestions should be in such form that a minimum of special technical knowledge is required of roentgenologists, since their time is usually fully occupied by clinical and administrative problems. This group of physicians constitutes a large majority of all of those concerned with the X-ray diagnosis of thoracic disease.

A summary of the work directed toward the two objectives described above follows in two sections:

1: Important factors in the choice of apparatus and technique for chest roentgenography.
2: Technical assistance for the roentgenologist in the choice and use of roentgenographic apparatus.

IMPORTANT FACTORS IN THE CHOICE OF APPARATUS AND TECHNIQUE FOR CHEST ROENTGENOGRAPHY

Many physical phenomena combine in the production of a finished chest roentgenogram. These phenomena cannot, in general, be analyzed separately since they are interdependent. To present clearly and concisely the important aspects of the problem requires, therefore, a careful choice and brief description of the major factors of the roentgenographic process. The minor factors of the process, while they cannot be ignored in a detailed analysis, are not pertinent to the present discussion.

Apparatus for chest roentgenography cannot be specified for a particular institution without a careful consideration of the number of patients in the institution and the amount of money available for the apparatus and its maintenance. It is possible, however, to specify certain minimum requirements below which the roentgenographic results will be of such quality that accurate diagnosis becomes difficult, if not impossible. Specifications for apparatus satisfying such minimum standards follow, together with a description of the important factors in its choice and use.

The apparatus for this chest roentgenographic installation may be conveniently divided into twelve items. These items follow, together with short comments concerning their relative importance.

1: A suitable power transformer and supply line to provide 220 volts alternating current to the roentgenographic apparatus: This system is required to transform alternating current at some voltage usually in excess of 2,000 volts, distributed by the power company, to 220 volts for operation of the X-ray equipment. The capacity of the transformer and line must be so chosen that the installation is at once economical and adequate. If this voltage varies excessively, roentgenographic results cannot be accurately predetermined.

2: A control stand, high-tension transformer and motor-driven rectifier for transforming 220 volts alternating current into pulsating unidirectional current with a maximum output voltage of 100,000 volts: This item comprises most of the parts included under the general title, *X-ray machine.* It should be capable of delivering, at peak voltages of 100,000 volts, an average current of at least 100 milliamperes to the X-ray tube in order to ensure that roentgenographic exposures may be made in 1/10 second or less. The control stand must contain an autotransformer, by which the X-ray tube voltage may be varied at will in steps not exceeding one kilovolt from approximately 40 kilovolts-peak to 100 kilovolts-peak. The use of a mechanical rectifier may be criticized on the grounds that such apparatus is obsolete. There are so many devices of this type in use, however, in small institutions, and the results are technically so satisfactory, that to call such apparatus obsolete is distinctly uneconomical. If the remainder of the items in this description are included the assembled apparatus will produce roentgenograms of good quality. Half-wave rectification is not recommended for chest roentgenography. It should be noted, however, that for equipment of larger capacity the thermionic valve tube is to be preferred to the mechanical rectifier as a means for transforming alternating to pulsating current.

3: A line-focus X-ray tube with an effective focal spot 3 millimetres square: Tubes of this size are capable of withstanding the exposures which can be made with the apparatus described in section 2 and will produce minimum unsharpness or blurring in the finished roentgenogram. It is required, however, that this tube be used at a focal spot-film distance of 4 to 5 feet, and it is *not* possible to obtain roentgenograms of good diagnostic quality with this apparatus at focal spot-film distances greater than 5 feet.

4: A low-tension cathode current stabilizer to maintain the temperature of a hot cathode (or filament) of the X-ray tube constant during the X-ray exposure: When an X-ray exposure is made, a series of pulses of current flows through the X-ray tube. The stabilizer ensures that all pulses of current have the same form and average value. It cannot ensure, of course, that the first and last pulses are identical with the others of the exposure. This latter is the function of the timer.

5: An impulse timer for making X-ray exposures of any of the following durations: 1/20 *second,* 1/10 *second,* 1/5 *second:* This device should be so constructed that, if the apparatus is supplied by alternating current having a frequency of 60 cycles per second (120 pulses to the X-ray tube per second), the 1/20-second exposure comprises precisely six identical pulses. Similary, the 1/10-second and 1/5-second exposures should comprise precisely twelve and twenty-four pulses, respectively. Impulse timers now manufactured are very expensive. It would be extremely helpful to small institutions having apparatus like that described in this section if a low-priced impulse timer with the three exposure times mentioned above were available.

6: An accurate means for adjusting and predetermining the temperature of the X-ray tube cathode: The adjusting device is usually mounted in the control stand. A cathode-current ammeter is usually used to predetermine the cathode temperature. These devices must be so designed that an accurate control of the cathode temperature is possible if roentgenographic technique is to be reproducible and if X-ray tube life is to be maximum.

7: A device for measuring the quantity of electricity which flows through X-ray tube during each exposure: This consists of a ballistic milliampere-second metre, mounted in the high-tension circuit, with a full-scale deflection of 25- or 50-milliampere seconds.

8: A tube stand with means for obtaining a vertical shift in the position of the tube between the exposures of a pair of stereoscopic roentgenograms: This device must be so constructed that the tube does not vibrate during exposure, and so that the tube may be universally adjustable for exposures at different distances and at different angles with respect to the X-ray film.

9: A cassette changer: The patient is placed before this device, and means are provided for removing one cassette from the field of the X-ray beam and placing a second cassette before the patient for making stereoscopic roentgenograms.

10: Cassettes with intensifying screens: The cassettes must be strong and light-tight, and the fronts of the cassettes must be made of material which absorbs relatively little radiation. The intensifying screens should be chosen to produce minimum unsharpness or blurring commensurable with a reasonable speed. The screens must be mounted so that they will be in intimate contact with the film throughout its area.

11: A properly equipped dark room: The dark-room illumination must be so designed that appreciable fog is not produced in X-ray films while they are being loaded in cassettes or processed. The processing tanks and film washing water should be maintained at a temperature of 65°F. plus or minus 2°F. Processing tanks should be covered when not in use, and fresh solution should be added to replace that which is lost by absorption by the film and by evaporation. Not more than one hundred and seventy-five 14-inch by 17-inch films should be developed in five gallons of solution, and the time of developing should be changed at the rate of one-half minute increase for every forty films.

12: Apparatus for viewing finished roentgenograms: Roentgenograms should be placed before uniform film illuminators, completely covering the source of illumination. The general intensity of light throughout the room should be relatively low (approximately 3- to 5-foot candles).

If the foregoing general recommendations are followed carefully, it is possible to produce high-quality chest roentgenograms and to reproduce roentgenographic results accurately. One other item of importance is the measurement of the patient's chest. This should be done in a carefully controlled manner and a full record kept of the measurements. Failure to do this makes it impossible to correlate technical data concerning roentgenographic output. The apparatus described in this paragraph satisfies minimum technical standards. With it chest roentgenograms may be made with a focal spot-film distance of 4 to 5 feet; exposure time 1/20 to 1/5 second; X-ray tube currents from 75 to 125 milliamperes; X-ray tube voltages from 50- to 90-kilovolts peak.

The installation described above does not, of course, produce roentgenograms of optimum diagnostic quality. In the following paragraphs

methods which lead to roentgenograms of the present highest standard are briefly described:

1: Apparatus of higher capacity than 100 milliamperes: Apparatus of this type should use full-wave valve tube rectification. Apparatus using four valve tubes, with a capacity of 300 or 500 milliamperes, may be used to enable the roentgenologist to reduce the exposure time to 1/30 or 1/20 second. This tends to reduce the blurring due to motion of the part roentgenographed. Machines employing six-valve tubes and three-phase alternating current are expensive. Furthermore, it is difficult to time short exposures accurately with this type of rectification. If condenser-discharge apparatus is to be used for chest roentgenography, present data indicate that the equipment should be constructed so that any one of the following capacitances may be chosen at will: $\frac{1}{4}$ microfarad, $\frac{1}{2}$ microfarad, 1 microfarad. Condenser-discharge machines having only one untapped condenser are not sufficiently flexible for chest roentgenography.

2: High-speed Potter-Bucky diaphragm: It is sometimes difficult to obtain a suitable roentgenogram of a part of the chest which absorbs a much higher percentage of radiation than normal. In such a case, improved results may be obtained by using a high-speed Potter-Bucky diaphragm synchronized with the X-ray exposure. Exposure factors are all kept constant except the X-ray-tube voltage, which is increased 15 kilovolts.

3: Device for obtaining exposures in the diastolic phase of the heart cycle: Chest roentgenograms synchronized in the diastolic phase are considerably less blurred by motion of the heart and vessels than are those taken at random cardiac phase. Furthermore, true stereoscopic films can be made only if the two exposures occur in the same phase of the cardiac cycle. Simple apparatus at a reasonable cost for accomplishing these purposes is in the process of development.

4: The rotating anode X-ray tube: Any method which will permit a reduction in focal-spot size for a given exposure will improve the sharpness in the finished roentgenogram. This may be accomplished by rotating the anode of the X-ray tube, so that different areas of tungsten are used for different parts of the exposure. Tubes of this type are quite expensive, but the technical advantages are easily recognized.

5: Stationary lead grid for absorbing secondary radiation: This device prevents a large portion of secondary radiation from striking the film. However, since the grid is stationary during exposure, shadows of the grid are produced in the finished film. This is distinctly a disadvantage, since it tends to prevent accurate delineation of the shadows of small parts of the lung structure.

6: Roentgenographic paper: It can easily be proved that a greater range of observed densities and greater observed contrasts may be produced by means of a roentgenogram made on a transparent film and viewed by transmitted light, than by a roentgenogram made on opaque paper and viewed by reflected light. The question remains as to whether sufficient information may be obtained with the paper to justify its use. No definite conclusions have been reached in the solution of this problem, although from the technical point of view paper is definitely inferior.

TECHNICAL ASSISTANCE FOR THE ROENTGENOLOGIST IN THE CHOICE AND USE OF ROENTGENOGRAPHIC APPARATUS

The analysis of apparatus and technique given in the second section of this paper is necessarily no more than a general summary. In any specific case, problems arise which require analysis by some one specially trained in this technical field. To help roentgenologists who want such advice a consulting service has been inaugurated. Any roentgenologist or sanatorium director interested in obtaining optimum-quality roentgenograms from his present apparatus, or in purchasing new equipment, or in solving special technical problems, may obtain this service. Efforts are being made continually to reduce the cost of such service.[3]

The technical methods upon which this service is based are continually undergoing improvements, with a view to attaining greater accuracy. The test equipment is so designed that it may be packed in an automobile for easy transportation. Two men are required to perform the tests in sanatoria. Their work requires from four to seven hours in the sanatorium, and approximately three or four hours for the analysis of data and the preparation of the report. An effort is made to present these reports in such form that the roentgenologist may carry out, according to his own judgment, one of two or three plans, any one of which will produce satisfactory roentgenographic results. An effort is made always

[3] Information concerning the plans of the service and their application may be obtained by addressing Mr. S. M. Sharpe, National Tuberculosis Association, 50 West 50th Street, New York City.

to take into account the importance of economy to sanatoria, although this factor cannot be permitted to compromise technical quality.

CONCLUSION

Work in this laboratory is directed in the manner described in this paper toward the following objectives:

1. Through the collaboration with roentgenologists information is available concerning the general criteria which should guide the roentgenologist in the choice and use of chest roentgenographic apparatus.

2. Simple brief analyses are presented, to acquaint the roentgenologist with those technical facts which he must have if he is to use his roentgenographic apparatus to greatest advantage.

3. A consulting service has been developed, through which the roentgenologist may discuss technical problems with those who have studied them carefully from a physical point of view, and by which he may obtain unbiased criticism concerning his apparatus and technique or concerning new apparatus which he may desire to purchase.

CONTRACEPTION IN THE TUBERCULOUS[1]

ERNEST S. MARIETTE[2]

Dr. Victor Pedersen begins his book, *Nature's Way*, as follows:

> No problem affects the welfare and happiness of the family more directly and intimately than the question of children. Perhaps no single advantage would increase the happiness of married couples so much as the power to regulate the size of their family according to their own desires and their capacity to provide adequately for such children as they may see fit to bring into the world. Such a power would certainly relieve thousands of married couples of the almost intolerable burdens of anxiety and fears and physical distress.

If this is true of the normal family when both parents are healthy, it is doubly true of a family in which either parent, particularly the mother, has a chronic disease like tuberculosis. That this occurs frequently is evidenced by the fact that "thousands of tuberculous women become pregnant and thousands of women of child-bearing age die from tuberculosis each year." Furthermore, from a perusal of the literature, it is apparent that more thought has been given to what to do after pregnancy has occurred than has been given to the problem of preventing it. This is not to be wondered at as physicians since the time of Hippocrates have been taught how to treat existing conditions rather than how to prevent their occurrence. To be sure, we warn tuberculous women of the possible consequences of marriage and we tell those who are married of the dangers of bearing children while their disease is active. But in doing so we give them little if any definite advice about the scientific methods of avoiding pregnancy.

Perhaps we can gain a better understanding of the entire problem of birth control in the tuberculous if we understand the nature of the tuberculosis problem, that is, how tuberculosis acts and how the body reacts to it. Tuberculosis is called an infectious rather than a contagious disease because it is spread chiefly through the sputum of the consump-

[1] Presented before the Minnesota Birth Control League, Minneapolis, Minnesota, April 26, 1935.

[2] Glen Lake Sanatorium, Oak Terrace, Minnesota, and Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

tive and through infected cow's milk. Therefore, in order to acquire infection, direct contact with the sick individual is not necessary, but contact with his sputum or with infected cow's milk is. As a result of the tuberculin-testing program of cattle with the eradication of the reactors and the pasteurization of all milk, the cow has been practically eliminated as a source of tuberculosis in the United States. This leaves the tuberculous individuals as the chief source of infection, and, in so far as we can control them and their sputum or the moisture from their nose and mouth, tuberculosis will disappear.

You who are gardeners know that a crop can be decreased or increased according to the amount of seed sown. The same general condition holds true for tuberculosis. Reduce the seed by diminishing the opportunities for infection and the crop or the incidence of tuberculosis is reduced also.

Gardeners also know that the condition of the soil has a great deal to do with the crop produced from the seeds planted. Here, too, the same general condition holds true for tuberculosis. There can be no other explanation of the fact that only about 2 to 10 per cent of those infected with tubercle bacilli ever develop the disease. The rest remain well. For this reason it behooves everyone to keep his or her body in such a good condition that whatever infection a person may acquire will have great difficulty developing into active disease.

In its effort to control a tuberculous infection, the body builds a wall or enveloping capsule about it. Whether or not active disease follows depends upon how firm and tight this wall is. In spite of the fact that from 90 to 98 per cent of those infected remain perfectly well, these areas of infection seldom heal completely. A few tubercle bacilli escape occasionally, but fortunately the resistance of the body has been so stimulated by this infection that it is very difficult for the bacilli to start a new lesion. If the infected individual did not have this ability to cope with fresh implantations of the bacilli, the white race would have been wiped out years ago when everybody was exposed to repeated infections.

During the long years of man's contact with tuberculosis he has had ample opportunity to form definite conclusions concerning the effect of pregnancy on the health of the consumptive. These conclusions have varied with his knowledge of tuberculosis. Because of the general improvement in the health of many normal women during pregnancy, the early writers advised pregnancy as a preventive measure for women whom they considered predisposed to tuberculosis. Even as late as the middle

of the last century physicians recommended pregnancy as a form of treatment for tuberculosis. This teaching is still accepted by some of the laity. One of the young women of our series believed this so firmly that, in spite of everything we could say, she left the sanatorium to become pregnant. While she was away from the institution, she received no treatment for her tuberculosis. Her condition was hopeless when she returned, and she died shortly after the birth of her baby.

In the early part of the twentieth century the pendulum swung to the other extreme. Those considered predisposed to tuberculosis or those in whom tuberculosis had already developed were cautioned against pregnancy and, if a pregnancy did occur which was discovered before the fifth month, a therapeutic abortion was advised.

From a study of the literature it is apparent that the conclusions upon which such advice was based were derived from a comparison of the pregnant women, tuberculous and nontuberculous. Such a comparson is obviously unfair because the tuberculous woman of childbearing age, whether pregnant or not, has a much higher death-rate than the non-tuberculous woman of the same age group.

In studying this problem in 1921, we came to the conclusion that the harmful factor in this combination was the tuberculosis rather than the pregnancy. Therefore, we felt that the emphasis in the treatment should be directed toward the tuberculous process rather than toward the pregnancy. Accordingly, we concluded that an abortion was not indicated. This represented quite a departure from the accepted teaching, and our first few cases who were carried to full term were watched with some anxiety, but in the end the results confirmed our belief. From September, 1921, to February, 1933, therapeutic abortion was advised among our pregnant tuberculous women only once. During that time 35 pregnant tuberculous women were allowed to go to full term. Of that number, 18 were classified as far advanced, 13 as moderately advanced, and 4 as minimal. Only three of this number died, and their deaths were known to be inevitable after the first month of observation. This gives us a death-rate of about 9 per cent in contrast to a death-rate of 29.6 for all women 20 to 50 years of age discharged since 1916. These 35 women, furthermore, gave birth to 37 healthy children.

In addition to these thirty-five, there were 13 pregnancies in which delivery was premature. In four it was premature because of spontaneous reasons, and in nine it was induced. The first pregnancy was interrupted therapeutically. Death followed. The second, an ectopic pregnancy, was operated on at the second month. The remaining seven

pregnancies were criminally aborted. As we did not advise an abortion, these patients obtained leaves of absence from the institution and had the abortion elsewhere. There was one death in this group. This makes two deaths in the group which were aborted, and gives a death-rate of 25 per cent in that group in contrast to a death-rate of only 9 per cent in the group allowed to go to full term. While this entire group is small, still, in our series, aborting the tuberculous pregnant woman proved to be more hazardous than allowing her to go to full term.

Therefore, our experience does not support the theory that the tuberculous woman should never become pregnant. Do not construe this to mean that we are advocating pregnancy, because we are not. We think it should be postponed until the proper time. But, if it does occur, we believe that an abortion is seldom if ever necessary.

Because so many women became pregnant while "on leave," it was apparent that the advice given them was inadequate. Therefore, certain of the physicians occasionally offered definite contraceptive information to those married women who had leaves of absence. Upon discharge, certain of them were referred to your clinic.

In order to make definite birth-control information available to all of the married women, arrangements were made in the fall of 1933 with the Minnesota Birth Control League, whereby two of our physicians could be trained in the method of birth control approved by the League. Since then, more and more of our married women have received definite contraceptive information. Some of our Staff are definitely opposed to this procedure, others are indifferent to it, while others are supporting it very actively. To secure a more uniform policy, the Social Service Department has been instructed to refer each married woman, who applies for a leave of absence, to the proper physician for birth-control instruction. If for any reason she does not desire it, the matter is dropped. Under this plan, tuberculous women who wish the advice are spared the prolonged treatment and the unnecessary hardship of a pregnancy.

Even though pregnancy, when properly treated, does not exert a particularly harmful influence on the already diagnosed tuberculosis, still it does impose an extra load on the patient, thereby prolonging treatment. It may also bring a child into a family which is ill prepared for it, thus retarding convalescence and increasing the possibility of relapses. Because of this we believe it is much more logical to restore the woman to health, and to keep her well for two or three years under normal conditions of life before permitting her to become pregnant.

Thus birth control, intelligently applied, will permit tuberculous women to marry earlier than they could otherwise.

There is still another aspect to this question and this is the economic side. According to statisticians, the tuberculosis death-rate in the unskilled laboring group is about six times greater than it is in the professional group. Also, it is about five times greater in those who are able to take out group insurance only than it is in the group able to carry individual policies of $5,000 or more. It is apparent, then, that most of the tuberculosis is found in those families in which overcrowding and underfeeding are most likely to occur. These are the families which would benefit greatly by scientific contraceptive advice, but because of their low wage-scale they rarely consult a physician. A clinic such as yours offers a solution for these families.

Some of our married-men patients now realize that, even though their wives are healthy, still another child should not be added until the head of the family can properly provide for it. Because of this, they are asking how such birth-control information can be secured for their wives. When such men have a private physician, we suggest that they send their wives to him. All others are given one of your regular clinic cards which introduces their wives at the clinic.

CONCLUSIONS

1. Our experience does not support the theory that the tuberculous woman should never become pregnant.

2. If a woman with active tuberculosis or recently arrested tuberculosis becomes pregnant, an abortion is seldom necessary.

3. While the pregnancy does not exert a particularly harmful influence on the already diagnosed tuberculosis, if that is properly treated, still it does impose an extra load on the patient and thereby prolongs treatment. Because of this, we believe that every tuberculous married woman should be given birth-control information, so that pregnancy can be postponed until, in the judgment of her physician, it can be undertaken with safety to the mother and child.

4. When any of our married women apply for a leave of absence, our Social Service Department refers them to the proper physician for birth-control instructions. If for any reason the woman does not desire it, the matter is dropped.

5. The married woman with tuberculosis must have more than an admonition to prevent pregnancy; she must have the best contraceptive advice available.

THE FILAMENT-NONFILAMENT COUNT IN TUBERCULOSIS COMPARED WITH THE SEDIMENTATION RATE AND THE LEUCOCYTIC INDEX[1]

DAVID PAINE[2] AND KATHERINE H. AUSTIN

In 1904 Arneth (1) divided polymorphonuclear neutrophiles into five classes according to the shape and number of divisions of the nucleus, grading them in relation to their degree of maturity. He originated the term "shift to the left."

Von Schilling (2) simplified this classification in 1920, dividing the cells into myelocytes, juvenile forms, and band forms.

In 1920 Farley, St. Clair, and Reisinger (3) further simplified the enumeration of immature leucocytes by dividing polymorphonuclear neutrophiles into what they called filamented and nonfilamented cells. A nonfilamented cell is a cell whose nucleus is either not divided at all or is divided and separated by a band of nuclear material of some thickness. The filamented cells are the mature cells, the nonfilamented, the immature. The authors found this count to be reliable as a diagnostic aid in many diseases, and Roberts (4), calling the cells lobulated and nonlobulated, found the count to be of value in inflammatory conditions.

Mullin and Large (5) reported the filament-nonfilament count in a series of patients with acute illnesses, and stated that it followed more closely the course of the infection than did the total leucocyte count. In their group the majority of patients whose blood showed over 50 per cent of nonfilamented cells proved to be fatally ill.

Several investigators have studied the immature leucocytes in tuberculosis. Ramel (6) reported that the shift to the left was more accurate than the sedimentation rate in tuberculosis. Marie Walter (7) found that a shift to the left was present in 86.2 per cent of her active cases of tuberculosis and absent in 15 inactive cases. She concluded, however, that absence of a shift to the left did not rule out activity.

Duffy (8) obtained, in a group of tuberculosis patients, a total of 51 instances of rise in percentage of immature polymorphonuclears; 16 occurred before signs of increased clinical activity and 19 without appar-

[1] From the Worcester County Sanatorium, Worcester, Massachusetts.
[2] Middlesex County Sanatorium, Waltham, Massachusetts.

ent clinical activity to account for the phenomenon. His study included a comparison with the sedimentation rate, and he observed that increase in the sedimentation rate occurred rather as a coincidence with and sequel to spread of disease than as an antecedent or early manifestation of impending relapse.

Cass (9) in 1934 reported a study of Schilling counts, leucocyte counts and sedimentation tests in 35 tuberculous patients at the Channing Home in Boston. His conclusions were that it is difficult to select one procedure as the ideal indicator of pathological activity but that properly performed sedimentation tests would probably give an accurate portrayal of the pathological state of the patient; that the chief help of blood studies is in determining when to return a patient to a normal regimen.

While these observers had applied the Schilling count to tuberculosis, Medlar (10) first used the filament-nonfilament modification in this disease, calling the cells segmented and nonsegmented. In patients seriously ill he found the nonfilamented neutrophiles to be consistently above normal. He considered a persistence of over 8 per cent of nonfilamented cells as abnormal, although all the cases cited in his paper as clinically active had percentages above 16. He found a marked fluctuation in the shift of the neutrophilic types from day to day. He says, "The change in the neutrophilic form may indicate the volume of leukopoietic tissue the individual case possesses more than the seriousness of the pathologic process."

Kelley (11) also studied the nonfilamented cells in tuberculosis, thought the count to be at least as reliable as the leucocytic formula, and believed that it sometimes yielded information that was not obtainable by any other method.

METHODS

The purpose of this study was to take comparative nonfilament counts, leucocyte counts, and sedimentation rates on a group of tuberculous patients over a considerable period of time, comparing the three tests as guides to pathological activity and as warning signals of approaching relapse, with particular emphasis on the nonfilament count.

In order to confirm the findings of previous workers, nonfilament counts were done on 50 healthy members of the sanatorium personnel. All were under 16 per cent, ranging from 2 to 16, with an average of 7.7 per cent. Thus we have used the base-line of 16 set by Farley, *et al.* (3) as the upper limit of normal rather than the 8 per cent suggested by Medlar (10).

The leucocyte and nonfilament counts were done on the same day from the same smear. Two hundred cells were counted, and the percentages given for nonfilamented cells are not the percentage of these in 100 neutrophiles but in 100 leucocytes of the various kinds, including neutrophiles, lymphocytes, monocytes, etc.

Following the criteria of Cooke and Ponder (12), if none of the bands of nuclear material connecting different parts of a nucleus of a cell was thicker than a chromatin filament, that cell was considered to be a filamented cell.

The Cutler (13) method was employed for the sedimentation tests, including his two-inch, one-cubic-centimetre tubes. Three per cent sodium citrate was used for dilution, in the proportion of one part citrate to nine parts blood. Readings were taken at the end of one hour. All the patients in this study being men, the upper limit of normal was considered to be 8 millimeters.

There were 77 patients of the Worcester County Sanatorium whose blood was studied, all of them men. Leucocyte and nonfilament counts were done every month. Sedimentation tests were performed less frequently,—an average of twice for each patient during the nine months during which the study was carried on, and whenever a marked change occurred in his pulmonary condition.

In order to facilitate comparison of the leucocytic reaction with the other tests, we have used the leucocytic index devised by Crawford (14) to simplify the interpretation placed upon Medlar's leucocytic reaction. This index includes the neutrophile-lymphocyte ratio together with arbitrary values for abnormal total counts and increased percentages of monocytes. The index is obtained by the use of their rotary-slide rule. The index number begins at zero as the most favorable and increases progressively to 100 plus. The values given by these authors for the index numbers are as follows: 0–15, favorable; 15–20, slightly favorable; 20–26, slightly unfavorable; 26–35, unfavorable; 35–100 very unfavorable. More detailed information can be found in the original article.

RESULTS

In table 1 the reader will find a rough comparison of the three tests. Table 2 shows the principal features of several typical cases in which the essential agreement of the three tests is evident.

There were 8 patients whose nonfilament percentages exceeded 50 on at least one occasion; all had very grave lung involvement; five died, and

the other three had a hopeless prognosis. In general, the height of the nonfilament percentage was roughly proportional to the amount and degree of activity of the disease. Of the positive sputum cases 95 per cent had elevated nonfilament counts. Of the negative sputum cases 63.5 per cent had normal nonfilament counts.

TABLE 1

Number of sedimentation tests	107
Percentage of sedimentation tests elevated	90.7 per cent
Number of nonfilament counts	395
Percentage of nonfilament counts elevated	68.5 per cent
Number of leucocytic indexes	395
Percentage of leucocytic indexes elevated	67.9 per cent
Number of times nonfilament count elevated when sedimentation rate normal.	6
Number of times sedimentation rate elevated when nonfilament count normal.	25
Number of times nonfilament count elevated when leucocytic index favorable.	45
Number of times leucocytic index unfavorable when nonfilament count normal	58

TABLE 2

Specimen cases showing agreement of the three determinations

PATIENT	CONDITION	NONFILAMENT COUNT	LEUCOCYTIC INDEX	TOTAL	LEUCOCYTE COUNT			SEDIMENTATION RATE
					Polys	Lymphos	Monos	
C. C.	Minimal A. Asymptomatic	16	14	7,000	61	34	1	6
E. D.	Mod. Adv. A. Asymptomatic	6	9.5	6,200	51	39	6	8
J. B.	Far Adv. C. Large cavities. Laryngitis. Pleural effusion. Died	47	64	18,600	68	14	17	27
M. G.	Far Adv. A. No cavities. Laryngitis	16	20	7,500	55	28	8	20
J. K.	Far Adv. A. Chronic empyema	31	35	10,000	69	20	10	17.5

There were 27 patients, afebrile and free from constitutional symptoms, whom we considered to be clinically inactive. None of these had nonfilament counts higher than 22 and most of them were under 16. Only five did not have favorable leucocytic indexes. Of these five, one was classified as slightly favorable, three slightly unfavorable, and one unfavorable. Nine of these 27 clinically inactive patients had elevated sedimentation rates, ranging from 10 to 22, but, in most of these, successive tests were progressively lower.

There were 12 patients with normal sedimentation rate, 24 with favorable leucocytic index, and 29 with normal nonfilament count. All were clinically inactive, and all were inactive by X-ray with one exception. The exception was a patient with a gradually enlarging cavity. His sedimentation rate and nonfilament percentage were elevated but his leucocytic index remained normal throughout the study.

Of the 77 patients there were only nine in whom the trends of the three tests were repeatedly in disagreement. It is apparent from table 3 that

TABLE 3

Patients in whom the three determinations were repeatedly in disagreement

PATIENT	CONDITION	NONFILAMENT COUNT	LEUCOCYTIC INDEX	TOTAL	LEUCOCYTE COUNT			SEDIMENTATION RATE
					Polys	Lymphos	Monos	
H. O.	Far Adv. A. No cavity. Clinically inactive	14	36	8,000	72	20	4	12
E. M.	Minimal A. Asthma	12	20	10,000	60	30	7	22
B. M.	Far Adv. A. Fibrocavernous disease. Chronic arthritis	6	11	8,000	50	32	7	22
L. W.	Mod. Adv. A. Relapse 16 days later	4	4.5	11,000	50	45	3.5	13
H. D.	Mod. Adv. A. Exudative infiltration with cavity. Retrogressive lesion	13	23	8,400	63	27	6	14
L. L.	Mod. Adv. A. Silicosis	15	3	6,300	45	40	10	12
J. P.	Far Adv. A. Draining chest sinus	12	23	9,000	60	26	8	16
E. P.	Far Adv. A. Slowly enlarging cavity	10	14	10,000	58	35	6	12
J. S.	Mod. Adv. A. No definite cavities	15	17	6,000	55	30	8	12

in all of them the sedimentation rate remained elevated while one or both of the cell counts were normal. Four of these had complications responsible for the elevation of the sedimentation rate, namely, arthritis, asthma, silicosis, and empyema with a chest sinus. Three were moderately advanced cases showing progressive clearing and organization of their disease. One had a slowly enlarging cavity and one had an extension of his disease 16 days later.

RELAPSES

Sixteen patients in the series showed steady progression of the lesion throughout the course of the study. In all of them, without exception,

nonfilament counts, sedimentation rates and leucocytic indexes were elevated.

It was hoped that the nonfilament count would surpass the sedimentation rate and the leucocytic index as a warning of coming trouble, but in the four patients tabulated in table 4, in whom new lung territory was invaded or a new cavity appeared during the study, it failed every time to show a warning increase. To be sure, all but one of these four patients had an elevated nonfilament count, but without exception the nonfilament count taken in the 7 to 31 days just preceding the exacerbation showed a fall instead of a rise. The sedimentation rate was elevated in every case but was not taken near enough to the time of the relapse to

TABLE 4

Patients showing sudden and marked relapse

	INITIALS OF PATIENT			
	E. J.	L. W.	H. A.	A. O.
Nonfilament count				
Previous	54	9	24	25
Preceding relapse	39	4	22	23
Following relapse	32	32	29	31
Leucocytic index				
Previous	76	0	61	35.5
Preceding relapse	78	4.5	34	35
Following relapse	89	33	42	27
Sedimentation rate				
Preceding relapse	26	13	30	24

demonstrate a comparative rise or fall. In three of the relapsing cases the leucocytic index was elevated before the relapse, but in the fourth (L. W. in table 4 and table 3) the index indicated a healing process. This case, relapsing soon after a normal leucocytic index, is similar to the three cited by Kelley (11) who were on exercise and had inactive leucocyte pictures preceding their relapses. It bears out, moreover, the statement of Cass (9) that prognosis is related to many mechanical and unforeseen factors, such as haemoptysis, rupture of a tuberculous abscess, etc. He found that counts done as often as every two weeks were not of value in prognosticating trouble but changed at about the same time or soon after a clinical upset.

The patient, L. W., above, is cited as relapsing in spite of a normal

leucocytic index. A glance at table 3, however, will show that although his differential count was good, with 50 per cent polys and 45 per cent lymphocytes, still his total leucocyte count was 11,000, not a normal figure.

DISCUSSION

The nonfilament count and leucocytic index were remarkably often in agreement. Certainly the nonfilament count in this study proved no more delicate than the leucocytic formula as an index of coming trouble. The sedimentation rate, as other observers have noted, sometimes remains high after the nonfilament count and the leucocytic index have returned to normal and the patient has become clinically inactive. The personal equation is a factor in doing nonfilament counts because many cells are hard to classify. This, however, is true also of the leucocytic index where the differentiation between monocytes and large lymphocytes is often difficult.

SUMMARY

1. Filament-nonfilament counts done on 50 normal people varied from 2 to 16 per cent, averaging 7.7 per cent.

2. Filament-nonfilament counts, leucocytic counts, and sedimentation tests were taken simultaneously at intervals on 77 tuberculous patients.

3. In only nine of the patients studied were the trends of the three determinations in disagreement. For the most part filament-nonfilament and leucocytic counts agreed closely.

4. In the 16 patients showing steady progression of the lung process all three tests were elevated consistently.

5. In 4 patients showing a sudden and marked increase of disease neither filament-nonfilament nor leucocytic index showed any premonitory rise.

6. Sedimentation rates remained elevated in some patients who were clinically inactive and whose leucocytic index and nonfilament count had returned to normal.

7. The filament-nonfilament count in this study demonstrated no superiority over the leucocytic index.

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THE AUTOURINE TEST IN THE DIAGNOSIS OF TUBERCULOSIS[1]

ERNEST B. HANAN AND SOPHIA ZURETT

The tuberculin reaction in man does not differentiate between the inactive and active disease processes. Any procedure or test giving promise of help in distinguishing between these phases of tuberculous infection is deserving of serious consideration. In 1919 Wildbolz (1) described such a test, based upon the principle that tuberculin-like substances of specific antigenic nature are excreted in the urine during the active stage of tuberculosis, but do not occur in arrested tuberculous infection. Since the publication of Wildbolz's original paper there have appeared in the literature at least forty-four papers dealing with some phase of this test, many with disparaging results. Gibson and Carroll (2) in 1921 were the first to report in this country on the clinical application of the test with satisfactory results. Korns (3) in 1923 applied the test to 81 cases, 33 of which were actively tuberculous and 48 nontuberculous. In this series he found 74 per cent agreement with Wildbolz. He discussed the test from a theoretical standpoint, and indicated the practical difficulties in applying the test after the Wildbolz technique. Hayman (4), in a series of 75 cases, found 80 per cent agreement with Wildbolz, and felt that a properly controlled positive reaction was indicative of active tuberculosis, but that a negative test was of less value unless repeated. In 1924 a thorough historical review of the literature was given by Enright and Rettger (5), together with their studies on the test which showed encouraging results.

The discovery of specific urinary antigens in other diseases lends further encouragement to studies on the Wildbolz reaction. In 1894 Griffiths (6) (7), following a series of studies, claimed to have isolated from the urine in cases of diphtheria, pneumonia, and scarlet fever, chemical substances characteristic of these infections. He concluded that in acute infectious diseases specific substances are excreted in the urine characteristic of the aetiological factor producing the disease

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process. Since the development of modern biological technique, Dochez and Avery (8) in 1917 confirmed this principle in pneumonia by demonstrating the type-specific pneumococcus antigen in the urine of patients suffering from this disease. Conybeare (9) in 1933 demonstrated the presence of scarlet fever toxin in the urine of patients ill with scarlet fever.

These results indicate a field of study which is comparatively neglected by the immunologist and pathologist, yet one that promises to increase our understanding concerning the reaction of the host to infection. These concepts have prompted the authors (10) (11) to undertake the following studies on the Wildbolz reaction. Furthermore, the divergence of opinion concerning the clinical value of the test suggested a study of the original technique with a view to the possibility of devising a more simple test.[2]

STUDIES ON THE WILDBOLZ AUTOURINE CONCENTRATION TEST

Since these studies were definitely along lines of diagnostic methods, it was deemed advisable to give special attention to the technical procedures employed by previous investigators.

The original test: Following carefully the original technique of Wildbolz (1), 150 cc. of freshly collected morning urine were placed in a 500-cc. vacuum flask attached to a vacuum pump capable of maintaining 25 to 28 inches of vacuum. After the maximum vacuum was established, the flask was placed in a water-bath at 100°C. Care was taken that the temperature within the flask did not go above 60°C.

When the urine was concentrated to 15 cc., it was cooled and filtered through filter paper impregnated with 2 per cent phenol. Five-hundredths cc. of the filtrate was injected intracutaneously into the forearm of the patient from whom the urine was obtained. In the same manner five-hundredths cc. of a 1-1,000 dilution of Old Tuberculin was injected below the urinary filtrate.

The interpretation of the skin reactions obtained with this technique offered considerable difficulty. There were variations in the type of skin reactions in different individuals. The main difficulty was due to the urinary salts which gave pseudoreactions and, in some cases, necrosis at

[2] The writers wish to express their appreciation to Dr. Donald McKay and Dr. Helen G. Walker of the Tuberculosis Service of the Buffalo City Hospital and to Dr. Clifford R. Orr, Roentgenologist, and Dr. William F. Jacobs, Pathologist, for their generous coöperation and interest in these studies.

the site of the injection. However, it was observed that these nonspecific reactions usually receded by the end of 48 hours, while the specific tuberculin reaction persisted from 3 to 14 days. In this respect the preliminary studies confirmed Enright and Rettger's criticisms of the test and also their explanations of the discrepancies in the results of previous investigators.

Enright and Rettger's modification: In order to eliminate the urinary salts, these investigators resorted to dialyzation of the urinary extract. Their technique was as follows:

One hundred and fifty cc. of fresh morning urine were concentrated in vacuo to 1/10 of the original volume. The concentrated urine was cooled one hour in an ice-box and then filtered through paper. The residue was washed with distilled water until the filtrate and washings totalled 15 cc. This filtrate was dialyzed in running water for 24 hours through a completely dried collodion tube that had been treated with 80 per cent alcohol. The dialyzed residue was concentrated to dryness *in vacuo* and taken up in 15 cc. of physiological salt solution. Five-hundredths cc. of this preparation was used for the skin test in individuals capable of reacting to a 1-10,000 dilution of Old Tuberculin.

These workers used this procedure in 30 cases of known tuberculosis and 16 healthy individuals. The tuberculous antigen was demonstrated in the urine of all patients with active tuberculosis, while the 16 healthy subjects were negative. The nonspecific reactions did not occur so frequently with the dialyzed extract.

After preliminary studies with the above technique it was used in the first part of the following investigations with slight modification as follows: To one hundred and fifty cc. of freshly collected morning urine a few drops of zylene were added to prevent foaming. This was concentrated *in vacuo* on a water-bath to 20 cc. The concentrate was then placed in a parchmentized diffusion shell (Whitman, size 16 x 100 mm.), that had been previously hardened in 10 per cent formalin, and dialyzed over night in running tap-water. The dialysate was concentrated just to dryness *in vacuo* and the residue suspended in 10 cc. of sterile physiological salt solution. This was then cooled in an ice-box and centrifugated. Approximately 0.1 cc. of the supernatant fluid was used for the skin test.

Administration of the test: It was found that the size of the skin bleb produced was a better index of the amount to inject than volume as

measured by the syringe. Selecting the flexor surface of the patient's forearm and using the intracutaneous technique, a 5-mm. bleb was produced near the wrist with sterile salt solution. This served as a control on both the patient's reaction to the salt and the cleanliness of the syringe. Then a 5-mm. bleb was produced just above the middle of the forearm, using the patient's urinary extract. Following this a bleb similar in size was produced, 1.5 inches above the urinary injection, using a 1-10,000 dilution of Old Tuberculin. Done in this order the same syringe was used for the entire test.

Interpretation of the test: After preliminary studies concerning the nature of the reactions and their relations to each other, it became obvious that three important factors were involved in the interpretation of the test when administered as above described. These factors may be expressed as follows:

1: During the first twelve or forty-eight hours the urinary tuberculin reaction may be obscured by a nonspecific or pseudoreaction due to other toxic substances that may be present in the urine, but such reactions tend to regress by the end of forty-eight hours while the specific tuberculin reaction remains.
2: The skin tuberculin reaction usually persists from four to seven days, and sometimes fourteen days or even longer. This gives time for the nonspecific reaction to disappear.
3: When a specific minor skin tuberculin reaction is near its homologous major reaction, the minor reaction tends to remain until the major reaction begins to regress. This was observed by Wildbolz (1) and confirmed by Gibson and Carroll (2).

These three factors have apparently not been sufficiently emphasized in the interpretation of the Wildbolz test. This would probably account for some of the divergences in the results of various investigators. The third factor is of special importance, since the urinary extract may contain but a small amount of the tuberculous antigen, but its reaction is usually in evidence until the Old Tuberculin reaction begins to regress. In a few of the cases studied, the urinary tuberculin became the major reaction, and, as evidence of their homologous specificity, it was interesting to observe that the Old Tuberculin reaction remained in evidence until the urinary tuberculin reaction began to regress.

Basing the final interpretation upon these three factors, the test is observed at a time when the major reaction, which is usually the Old Tuberculin, begins to fade. This usually occurs on the fourth day. If

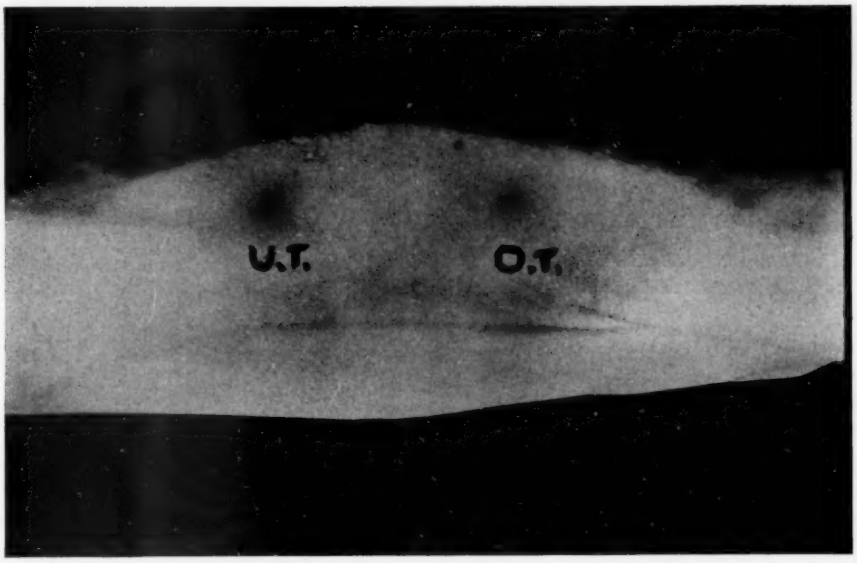

Fig. 1. Photograph of a typical autourine skin reaction on the forearm of a patient with active tuberculosis. *O.T.*, old tuberculin; *U.T.*, urinary tuberculin

TEST MATERIAL	FOREARM	NO Tb.	INACTIVE Tb.	ACTIVE Tb.
OLD TUBERCULIN 1-10,000	•	−	+	+
URINARY EXTRACT	•	−	−	+
SALINE CONTROL	•	−	−	−

INTERPRETATION OF THE AUTO-URINE TEST IN THE DIAGNOSIS OF TUBERCULOSIS (Tb)

CHART 1

the urinary reaction is still in evidence the result is interpreted as active tuberculosis. A photograph of a typical reaction is shown in figure 1. On the other hand, if the Old Tuberculin is positive and the urinary

tuberculin negative, the interpretation is inactive tuberculosis, but, if both are negative, then it is assumed that the patient has never had a tuberculous infection. The scheme of interpretation is shown in chart 1.

The degree of reaction was read as follows: erythema, 1 plus; erythema with induration, 2 plus; erythema with induration followed by vesiculation, 3 plus; and erythema with induration followed by ulceration, 4 plus.

The method used for reporting the results to the physician is shown by form 1.

Form 1

Autourine Test for Tuberculosis

Name..... Ward..... Date.....

Date of administration.....

Date read.....

Results: O.T. (1–10,000).....
U.T.....
Control.....

Interpretation.....

Form used for reporting results of autourine test for tuberculosis to the physician

Clinical application of the test: Using the previously described modification of the Enright-Rettger (5) technique, the test was performed on 147 hospital cases with the results as shown in table 1.

The 71 cases of tuberculosis classified as far advanced represent bilateral lung involvement with cavitation, or pulmonary involvement complicated by tuberculosis in other body tissues. Both the O. T. and U. T. reactions were negative in one case that was moribund, while the O. T. was doubtful in one and the U. T. was doubtful in four. In 66 of the cases the test was positive for active tuberculosis.

The 14 moderately advanced cases represent pulmonary involvement without cavitation. The U. T. was doubtful in one. In 13 of these cases the test was positive for active tubrculosis.

The 23 border-line cases showed only the clinical and X-ray signs of moderate degree as evidence of active tuberculosis. In two of these cases the O. T. was negative; the U. T. was doubtful in two and negative in nine. Subsequent check, as will be described later, has shown the 9 negative U. T. cases to be those of inactive tuberculosis.

In the disease processes classified as other than tuberculosis each of the 19 cases were suspected of having tuberculosis at one time or another during their stay in the hospital but subsequent diagnostic studies appear to have ruled out such condition. The O. T. was negative in 10 while the U. T. was negative in 17, doubtful in one, and positive in one. There is no definite explanation for the strong positive U. T. case; however, it is possible that there was at the time an active and hidden focus of tuberculous activity.

The 20 normal subjects were nurses and laboratory workers. The U. T. was negative as shown in all of these cases.

For a more thorough analysis of the results tabulated in table 1 it seemed advisable to compare the U. T. results with X-ray studies, and

TABLE 1

147 cases: showing the results of the autourine test for tuberculosis: O.T. old tuberculin, U.T. urinary tuberculin

CLASSIFICATION	NUMBER OF CASES	O.T. (1–10,000)						U.T.					
		++++	+++	++	+	?	–	++++	+++	++	+	?	–
Far advanced	71	1	3	31	34	1	1		6	15	45	4	1
Moderately advanced	14		3	5	6				2	6	5	1	
Border-line cases	23		3	12	6		2		1	4	7	2	9
Diseases other than tuberculosis	19	1		7	1		10			1		1	17
Normals	20	1	6	9	1		3						20

clinical laboratory and autopsy findings in relationship to the O. T. reaction. This was done under three headings: (1) those cases showing both negative O. T. and U. T. reactions or nonallergic cases; (2) those showing a positive O. T. and negative U. T. reaction; and (3) cases on which biopsy or necropsy studies were available.

The nonallergic group thus studied comprised 13 cases: the 10 classified under diseases other than tuberculosis, 2 border-line cases, and 1 classified as far-advanced tuberculosis as shown in table 1. The results are tabulated in table 1A.

In this group, case 211,716 is the only one showing active tuberculosis; but, as previously mentioned, this patient was moribund, and it is well known that the routine 1-10,000 dilution of O. T. frequently fails to elicit reactions in such conditions. Case 48,039 H has attracted considerable attention and is considered to be Besnier-Boeck's (12) disease. In

TABLE 1A

13 non-allergic cases: comparison of autourine test for tuberculosis with clinical and other laboratory findings in the diagnosis of tuberculosis (Tb.)

HOSPIAL FILE NUMBER	ADMISSION DIAGNOSIS	AUTOURINE TEST		X-RAY FINDINGS	PARTS X-RAYED	ACID-FAST BACILLI	CLINICAL ANALYSIS
		O.T.	U.T.				
236717	Myocarditis	Neg.	Neg.	None			Myocarditis: died
255145	Chr. pul. fibrosis	Neg.	Neg.	None		Neg.	Pulmonary fibrosis
47834 H	Chr. pul. Tb.	Neg.	Neg.	Neg.	Lungs	Neg.	Acute bronchitis
186495	Arthritis of spine	Neg.	Neg.	Neg.	Lungs	Neg.	Arthritis of spine
263864	Chr. pul. Tb.	Neg.	Neg.	Pos.	Lungs	Neg.	Moniliasis: improved
69921	Chr. alc. poisoning	Neg.	Neg.	Neg.	Lungs	Neg.	Pulmonary fibrosis
31206	Bronchiectasis	Neg.	Neg.	Neg.	Lungs	Neg.	Bronchiectasis
48039 H	Acute bronchitis	Neg.	Neg.	Neg.	Lungs	Neg.	Besnier-Boeck's disease
141721	Multiple sclerosis	Neg.	Neg.	None			Multiple sclerosis
211716	Lumbar abscess	Neg.	Neg.	Pos.	Lungs	Lumbar pus pos.	Moribund: died: retroperitoneal Tb.
100791	Bronchiectasis	Neg.	Neg.	None			Bronchiectasis
350930	Chr. epididymitis	Neg.	Neg.	None			Chronic epididymitis
356070	Serofibrinous pleurisy	Neg.	Neg.	Neg.	Lungs		Serofibrinous pleurisy: recovered

TABLE 1B

14 cases with positive O.T. and negative U.T.: comparison of autourine test for tuberculosis with clinical and other laboratory findings in the diagnosis of tuberculosis (Tb.)

HOSPITAL FILE NUMBER	ADMISSION DIAGNOSIS	AUTOURINE TEST		X-RAY FINDINGS	PARTS X-RAYED	ACID-FAST BACILLI	CLINICAL ANALYSIS
		O.T.	U.T.				
240639 H	Bronchial asthma	++	Neg.	Suspicious	Lungs	Neg.	Hilum Tb., apparently arrested
166906	Auric. fibrillation	++	Neg.	Neg.	Lungs	Neg.	Chr. myocarditis
56251	Chr. pulm. Tb. (?)	+	Neg.	Neg.	Lungs	Neg.	Chr. pul. fibrosis
250920	Pleurisy l. base	+	Neg.	Neg.	Lungs	Neg.	Chr. fib. pleurisy
199950	Poss. Tb.; pregnancy	+	Neg.	Suggestive bronchiectasis	Lungs	Neg.	Recovered
210473	Chr. myocarditis	++	Neg.	Neg.	Lungs	Neg.	Pulmonary fibrosis
238466	Chr. fib. pul. Tb.	+	Neg.	Neg.	Lungs	Neg.	Pulmonary fibrosis
254074	Intestinal Tb. Pulmonary Tb. (?)	+++	Neg.	Neg.	Lungs	Neg.	Impetigo simplex; recovered
238453	Pulmonary fibrosis	++	Neg.	Pos.	Lungs	Neg.	Bronchiectasis; rec.
259536	Chr. pul. Tb.	++	Neg.	Neg.	Lungs	Neg.	Chr. pul. Tb.; apparently arrested
191211	Chronic salpingitis	+++	Neg.	None			Chr. salpingitis; rec.
255196	Pulm. haemorrhage	++++	Neg.		Lungs	Neg.	Moniliasis
240139	Secondary anaemia	+	Neg.	Neg.	Lungs	Neg.	Autopsy; portal phlebitis
116198	Undetermined	++	Neg.	Neg.	Lungs	Neg.	Hypoglycaemia

this case, undiluted O. T. has consistently failed to give a reaction even when applied directly to the skin lesions.

The group showing positive O. T. and negative U. T. was comprised of 14 cases classified in table 1 under diseases other than tuberculosis and border-line cases. The results are tabulated in table 1B. Active tuberculosis has not been detected in any of these cases, even after a final check on available hospital records at the end of five years after the autourine test was performed.

Biopsy or postmortem findings are available in 9 cases. The results are tabulated in table 1C. These results are in agreement with the autourine test interpretations, and in three of the cases, 245,046, 239,858 and 241,988, the test gave the first evidence of the aetiological nature of the illness.

Further analysis shows that a positive U. T. reaction does not occur with a negative O. T. This would appear to be strong supportive evidence for the specificity of the test reaction.

Also, if one takes into consideration the 85 definitely known cases of tuberculosis in which one negative and five doubtful U. T. reactions were obtained (classified as far advanced and moderately advanced, table 1), the percentage of error is estimated to be about 8 per cent.

If the 147 cases are taken into consideration, in which 8 doubtful, one false negative and one possibly false positive occurred, the percentage of error is again approximately 8 per cent. There are very few clinical laboratory procedures that give a higher percentage of agreement with the final clinical evaluation of a disease condition.

It was further observed that the specific skin reactions were more definite in individuals with normal than in those with impaired skin. This would indicate that more definite skin reactions may be expected in early tuberculosis than in the far-advanced phases of the disease when the skin is poorly nourished. This is a distinct advantage for the test from a diagnostic standpoint.

Though these results were encouraging, it was felt that the test could not be practical for clinical application because of the tedious procedure involved in the concentration and dialyzation of the extract. The task was to develop, if possible, a more simple test procedure. It was thought that this could be achieved only by some procedure not requiring the concentration or dialyzation steps. Various protein precipitants were tried but discarded in favor of extraction or adsorbent reagents.

TABLE 1C

9 postmortem cases: comparison of autourine test for tuberculosis with clinical and other laboratory findings in the diagnosis of tuberculosis (Tb.)

HOSPITAL FILE NUMBER	ADMISSION DIAGNOSIS	AUTOURINE TEST		X-RAY FINDINGS	PARTS X-RAYED	ACID FAST BACILLI	BIOPSY OR AUTOPSY FINDINGS
		O.T.	U.T.				
74236	Chr. pulm. Tb.	+ 9–1–31	++	Pos. 9–1–31	Lungs	Pos. 9–5–31	12–11–31. Chr. pulm. Tb. with bronchogenic spread
242606	Pulmonary fibrosis	++ 6–6–31	++	Pos. 6–2–31	Lungs	Pos. 6–2–31	1–1–32. Chr. pulm. Tb. with Tb. enterocolitis
166644	Chr. pulm. Tb.	++ 6–29–31	+	Pos. 1–7–30	Lungs	Pos. 1–25–30	2–13–32. Chr. pulm. Tb. with bronchogenic spread
245046	Chr. salpingitis	+ 7–24–31	++	Neg.	Lungs	Neg.	8–26–31. Tb. salpingitis with Tb. peritonitis and miliary spread to lungs
221587	Chr. pulm. Tb.	+ 8–3–31	+++	Pos. 5–29–31	Lungs	Pos. 7–31–31	8–6–31. Chr. ulcerative pulm. Tb. with bronchogenic spread
239858	Pleurisy with effusion	+ 2–22–31	+	Pos. 4–2–31	Lungs	Pos. 4–24–31	10–11–31. Chr. pulm. Tb. with Tb. peritonitis
240139	Secondary anaemia	+ 10–20–31	0	Neg.	Kidneys; gastro-intestinal	Neg.	12–8–31. Portal phlebitis with thrombosis and intrahepatic multiple necrosis of liver
241988	Possible Hodgkin's	++ 5–31–31	++++	Neg.	Lungs	Neg.	6–11–31. Biopsy; Tb. cervical adenitis. Died 9–9–31. Tb. lymphadenitis with Tb. peritonitis and miliary spread
239019	Pulmonary Tb.	++ 6–9–31	+++	Pos. 4–22–30	Lungs	Neg.	Biopsy; Tb. lymphadenitis. 5–4–31

THE ETHER-CHLOROFORM AUTOURINE TEST

Since there are no known chemical tests for the identification of tuberculin-like substances, the determination of the extraction efficiency of any reagent used for its recovery presents considerable difficulty. It is necessary to work with known concentrations of the known antigen under known conditions, and then test for recovery of the antigenic principle by complement-fixation or skin tests.

Preliminary studies: It was found that the fat solvents gave promise of serving as reagents capable of extracting tuberculous antigen from the urine. Ether, chloroform, benzene, carbon-tetrachloride and equal parts of ether and chloroform were tested.

The following procedure was employed: 1 mgm. of ultraprotein tuberculin prepared after the method of Seibert (13) and furnished by Parke, Davis & Co. was dissolved in 150 cc. of distilled water. In order to test the reaction at which maximum recovery could be obtained, this was made slightly alkaline or slightly acid, as desired. Fifty cc. of the reagent was added, and the mixture shaken vigorously in a mechanical shaker for 10 minutes. The emulsion was then placed in a separatory funnel. When separation appeared, the reagent was drawn into an evaporation dish and evaporated to dryness over a water-bath. The residue, if acid, was made neutral with sodium bicarbonate and suspended in 10 cc. of sterile salt solution. One-tenth cc. of this extract was skin-tested on normal individuals and controlled with injections of known tuberculin. In order to have a reliable comparison, the various extracts were tested at the same time on the same individual.

Four or five normal individuals were selected for each test series, and the dilutions used were such as would not likely result in too serious a reaction. The results obtained are listed in table 2.

The ether and chloroform mixture apparently gave the most promising results and it is estimated that about 10 per cent of the original skin antigenic principle was recovered. This was considered to be a small amount but the simplicity of the test when compared with the Enright-Rettger procedure (5) encouraged its application to clinical studies.

Technique of the ether-chloroform autourine test: The procedure employed was as follows: 150 cc. of freshly collected morning urine were made slightly alkaline to litmus with sodium bicarbonate. Fifty cc. of ether and chloroform in equal amounts were added, and the mixture shaken vigorously in a mechanical shaker for 10 minutes. The emulsion was placed in a separatory funnel and when the separation appeared the

TABLE 2

Comparison of skin reactions on 14 normal individuals, showing recovery efficiency of known amounts of tuberculin by various extractive reagents

REAGENT	TEST DILUTION	INDIVIDUALS TESTED AND TEST REACTIONS													
		Slightly alkaline reaction										Slightly acid reaction			
		1	2	3	4	5	1	2	3	4	5	1	2	3	4
Ether	1–5,000	+	−	+	−	−	−	±	−	−	−	+	+	+	+
Chloroform	1–5,000	+	−	±	−	−	±	±	−	±	−	−	+	+	+
Benzene	1–5,000	±	−	+	−	−	±	±	±	±	+	−	+	−	+
Carbon tetrachloride	1–5,000	−	−	±	−	−	−	±	−	−	−	−	±	−	−
Ether and chloroform, equal amounts	1– 5,000	+	−	++	−	−	+	+	±	+	±	+	++	++	+
Controls O.T.	1–10,000	++	−	++	−	−									
Controls U.P.T.	1–50,000						++	++	++	++	++	+	++	+	+

TABLE 3

Routine autourine tests for tuberculosis on 206 cases using the ether-chloroform method

CLASSIFICATION	NUMBER OF CASES	O.T. (1–10,000)					U.T.				
		++++	+++	++	+	−	++++	+++	++	+	−
Far advanced											
Cavitation over 2.5 cm. or extensive double-lobe infiltration or complication with other types. Positive sputum	24		31	13	8			1	3	19	1
Moderately advanced											
Cavitation below 2.5 cm. or consolidation not below 3rd rib. Positive sputum or animal inoculation	21	1	3	13	3	1		3	2	11	5
Border-line cases											
X-ray infiltration alone or clinical evidence alone	63	2	18	32	4	7		4	15	15	29
Diseases other than tuberculosis	80	1	13	32	9	25		4	6	3	67
Normals	13		1	7	2	3					13
Unclassified suspected	5		2	2	1				2	3	

extractives were run into a dish and evaporated just to dryness on a water-bath. The residue was suspended in 10 cc. of sterile salt solution. Approximately 0.1 cc., or a sufficient amount to produce a 5-mm. skin bleb, was used for the test. The procedure of administration and interpretation of the test were the same as previously described.

Clinical application: If the autourine test is to be of any practical help in the diagnosis of tuberculosis, it must be in the border-line case. In order to secure these cases, a test was done on patients only on request of their physician.

It also seemed that the practical evolution of a test could be better obtained by its application in other hands than its originators; so the procedure was placed on a routine basis. The preparation of the urinary extract was done by a technician in the laboratory. The extract was then given to the resident physician, who administered it and interpreted many of the reactions. The results obtained on 206 cases are shown in table 3.

Considering the 45 cases of definitely known tuberculosis classified as far advanced and moderately advanced, in which six negative U. T. reactions were obtained, the percentage of error is about 13 per cent. In the 63 border-line cases, the test was positive for tuberculous activity in 34 and negative in 29. In the 80 cases of diseases other than tuberculosis, the test was negative in 67 and positive in 13. Two of these cases have since been autopsied. In one of these the pathologist was able to demonstrate foci of active tuberculosis, but active lesions could not be found in the other one. The possibility of small active tuberculous lesions in some of the remaining 11 cases must be considered. The 13 normal individuals gave negative reactions, but the five unclassified suspected cases which gave positive reactions are now considered clinically to be bone or joint tuberculosis.

While the results of these studies were not entirely gratifying, they do appear to indicate the importance of this line of investigation.

GENERAL DISCUSSION

The fact that specific antigenic substances occur in the urine of patients suffering from infectious diseases, as previously mentioned, tends to establish the theoretical soundness of the Wildbolz test.

The dialyzed material obtained from the urine by the Enright-Rettger procedure (5) is probably a mixture of nitrogenous substances, mainly proteose-like substances, toxins and various end products of proteins

resulting from body metabolism. The present form of the test and the many sources of error involved have caused considerable confusion among different investigators concerning its specificity for active tuberculosis. Most of the confusion is probably due to the presence in the urine of at least two groups of nitrogenous substances capable of giving skin reactions.

The first reaction usually occurs within 1 to 24 hours. It is erythematous in nature, spreading rapidly and fading within 24 to 48 hours, and leaving no apparent tissue damage. This type of reaction frequently occurs with the autourine extracts from normal individuals, and, as previously described, was termed a pseudoreaction. It is apparently due to proteose-like substances. Zinsser (14) showed that the proteose-like fractions extracted from the tubercle bacillus may retain antigenic activity, but one would not expect this property to be present after passage through the body tissues.

Oriel (15) and others (16) (17) claimed that "proteose" obtained from the urine of protein-sensitive asthmatics during their attacks gives specific skin reactions. Freeman (18) was unable to support their contention, and the authors have not observed any specificity of the "proteose" fraction in relation to tuberculosis, but this problem needs further study.

Seibert (19) has shown that tuberculin protein, when acted upon by digestive enzymes, is broken down to proteose and amino acids, with a corresponding loss of antigenic property. Long and Seibert (20) have also shown that acid hydrolysis of the tuberculin-protein molecule to proteose and amino acids results in loss of the antigenic activity. Thus, it would be expected that any protein tuberculin-like substances liberated from the tubercle bacillus in the tissues of the body would be subjected at least to similar enzymatic or hydrolytic action, with similar loss of specific antigenic character of the end-products as excreted in the urine.

The second group of substances in the dialyzed autourine extract capable of giving a skin reaction shows more evidence of tuberculin-like specificity. While reacting on tuberculin-sensitive individuals within 12 to 24 hours, it tends to remain localized, producing erythema and induration. The amount present may be so small that only erythema results. But, as shown in some of the tests, the amount recovered may be greater than a 1–10,000 dilution of O. T. This, however, occurred only when kidney damage was present, as evidenced by albuminuria. This type of reaction, even though erythema alone is present, remains in

evidence for four days, or until the O. T. control begins to regress, and it rarely occurs in individuals without tuberculous activity. It is conceivable that similar reactions may occur with urinary extracts from patients infected with *B. typhosus*, *B. mallei* or *B. abortus*. Such cases, however, are few, and other diagnostic procedures are available to rule out such conditions.

Most investigators have interpreted the results of the test at the end of 24 or 48 hours. This apparently does not allow sufficient time for the pseudoreaction to fade. It would also account for many of the discrepancies in the results reported by various observers.

Very little is known concerning the nature of the urinary tuberculous antigen. Enright-Rettger (5) and others (21) have isolated it in sufficient purity to study it by the aid of complement-fixation and skin tests. The authors, using different methods of isolation, have carried out similar studies with similar results and hope to report their findings at a later date.

The results of these studies indicate that the biological properties of the urinary tuberculous antigen appears to be similar to O. T.

Considerable criticism may be offered concerning the efficiency of a fat solvent, such as the ether-chloroform mixture for the recovery of a tuberculous antigen from an aqueous solution. However, it must be borne in mind that the work of different investigators (22) (23) (24) on the chemical nature of tuberculin shows that the crude tuberculous antigen is a mixture of proteins, lipoids and carbohydrates. As far as we know, a similar product may be liberated by the tubercle bacillus in the body tissues. It is possible that the lipoids and carbohydrates may be excreted in the urine with less modification of antigenic structure than would be expected to occur with the protein portion.

The "proteose" which gives the primary or pseudoreaction is not soluble in the ether-chloroform mixture; thus this substance is not present in sufficient amount in the autourine extract to cause serious confusion. The lipoids are soluble, as are possibly the carbohydrates to some extent. The jelly-like emulsion formed by agitation of the mixture in aqueous solution may secondarily act as an adsorbent for some of the less modified protein, especially if it is attached to a lipoid molecule of the antigen. A small amount would probably be caught in the water phase of the emulsion.

It may well be reasoned that these physical factors in the test procedure account for the estimated 10 per cent recovery as shown in table 2.

The weakness of the skin reactions obtained experimentally, and with the clinical application of the test, indicates the need of a more efficient extraction procedure.

These studies may be considered as preliminary. However, the authors feel that the Wildbolz reaction, properly controlled, is due to a specific tuberculous antigen in the urine and that the demonstration of its presence is good evidence of tuberculous activity. It is apparent that the recovery of such an antigen from the urine by the ether-chloroform method is too weak, thereby endangering a negative reaction in the presence of tuberculous activity in a border-line case, but the results appear to demonstrate clearly the direction in which studies should be made in order to isolate the antigen and elaborate a more simple and efficient test.

SUMMARY

1. It is suggested that more careful studies on the chemical and biological nature of the antigenic substances excreted in the urine from individuals with infectious diseases would increase our understanding of the immunology and pathology of these diseases.

2. The technique for the administration of the autourine test for tuberculosis and the factors involved in the interpretation of the skin reactions are described.

3. Two types of autourine skin reactions are described, and theoretical considerations concerning the specificity of the tuberculous urinary antigen are discussed.

4. The Enright-Rettger modification of the Wildbolz autourine test for tuberculosis was applied to 147 cases of known and suspected tuberculosis, with 92 per cent agreement with the final clinical and laboratory analysis.

5. A simplified procedure for the autourine test, using a mixture of ether and chloroform for extraction of the tuberculous antigen, thus eliminating the complicated steps of concentration and dialyzation of the urine, is described.

6. The ether-chloroform autourine test for tuberculosis was applied to 206 cases. The test was positive in 87 per cent of 45 of the cases known to have active tuberculosis. In 63 border-line cases the test was positive for active tuberculosis in 34, and negative in 29. In 80 cases of disease other than tuberculosis the test was positive for tuberculous activity in 13 and negative in 67. The test was negative in 13 normal individuals and positive in 5 cases of bone-and-joint tuberculosis.

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THE DESENSITIZATION OF TUBERCULOUS GUINEA PIGS WITH UNHEATED TUBERCULIN[1,2]

ARNOLD BRANCH AND G. V. KROPP

The observation that tuberculous guinea pigs can be rendered less sensitive to products of the tubercle bacillus on repeated increasing doses of "tuberculin" of one form or another is not new. Burnet (1) in 1908 was probably the first to show, using *tuberculin precipité*, which in a subcutaneous dose of 30 mgm. killed nontreated tuberculous guinea pigs, that other animals of the same group could be made to tolerate in a comparatively short time as high a dose as 200 mgm. Comparable results have been obtained by numerous observers since, using various "tuberculins" and products of the tubercle bacillus (Sorel (2), Manaud (3), Krause (4), Weinzirl (5), Boquet (6), Rothschild, Friedenwald and Bernstein (7), Derick, Branch and Crane (8), *et al*). In some instances the skin test was used as the test of desensitization and in others the general reaction. The route of inoculation has nearly always been subcutaneous, and of the materials used there have been few which were not subjected to rather severe chemical or physical treatment. In view of the fact that Seibert (9) has shown that the tuberculoprotein molecule loses its antigenicity if heated or treated with strong acid, it appeared to us worth while to use as the desensitizing agent an unheated tuberculin made from Long's synthetic medium. It is true that Weinzirl used a dialyzed Long synthetic medium filtrate and Rothschild and his coworkers some of Seibert's protein with no more favorable results than with other agents (O. T., acetone precipitated protein and tuberclebacillus vaccines prepared in various ways). We, however, desired to compare the intravenous with the subcutaneous route of inoculation and at the same time to be guided in our increase of dose by the general (thermal) as well as the local reaction. This enabled us to treat each guinea pig as an individual rather than as one of a group all similarly treated.

[1] From the Research Laboratories, Parke, Davis & Company, Detroit, Michigan.

[2] Read at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

MATERIAL AND METHODS

The guinea pigs were a mixed lot of both sexes, weighing 400 to 500 gm. The strain of H37 used for infection was an old laboratory one which in the dose used, 0.01 mgm. subcutaneously, did not prove to be as virulent as those we had previously employed. The *tuberculin* employed for desensitization and skin-testing was made from old cultures of the homologous organism grown on Long's synthetic medium. The organisms were filtered off through coarse and fine filter paper, and phenol was added to make a final concentration of 0.5 per cent. This was allowed to stand several weeks at room temperature, when the supernatant liquid was withdrawn and bottled in 50-cc. lots. Concentration in the incubator had occurred to half the original volume of the medium. Skin tests in three tuberculous guinea pigs with 1 per cent dilutions of this tuberculin and standard Parke, Davis & Company Human O. T. gave comparably intense necrotic reactions. A dose of 2 cc. invariably killed tuberculous guinea pigs on intravenous inoculation. One animal died after an initial intravenous dose of 0.1 cc. Normal animals sometimes gave a temperature reaction after 2 cc. intravenously. The tuberculin was also capable of rendering anaphylactic and shocking a normal pig. The intravenous inoculations were made with a 26-gauge needle into the veins of the extremities, the animals being first lightly etherized and a small superficial incision made with a razor blade through the skin over the vein. The subcutaneous inoculations were made over the abdomen and chest, a different site being exposed each time. The controls were etherized the same number of times as the treated subjects for approximately as long periods.

EXPERIMENTAL

On September 17, 1934, fifty guinea pigs were inoculated subcutaneously with 0.01 mgm. H37. Six weeks later they were skin-tested with 5 per cent unheated tuberculin. All the animals were skin-test positive, the majority strongly so. Eleven of the strongly positive reactors were used for testing the properties of the unheated tuberculin used in these experiments and for other purposes only indirectly connected with the desensitization experiment proper. The remaining 39 animals were divided into two groups. Twenty of these, including all but one strong reactor, were set aside for treatment with tuberculin, ten subcutaneously and ten intravenously. The remaining 19 animals were kept as con-

trols. In this latter group all but three were strong reactors. Eight days later (November 6) the proposed course of tuberculin was started. Before this, three control animals were killed and one died. At autopsy only one of the four had tuberculous lesions in the viscera; in the other three they were limited to the local site and lymph nodes.

THE INITIAL DOSE

In view of the finding from preliminary trial that 1 cc. of the tuberculin intravenously gave a rise of temperature in two animals of the same group but did not kill, it was considered safe to use 0.1 cc. as the first dose. Accordingly, fifty days after infection, all the animals were inoculated, ten subcutaneously and ten intravenously, with 0.1 cc. of tuberculin. One of the animals (C-11), inoculated intravenously, died the following night with the characteristic fall in temperature associated with tuberculin shock, preceded, however, by a preliminary rise in temperature which did occur in animals given large (2 cc.) fatal doses (chart 2). Seventeen of the remaining 19 animals showed a marked rise in temperature (104°–106°F.). This reached its maximum in 4 to 6 hours, occurring somewhat earlier in the intravenously than the subcutaneously inoculated group. It would be preferable in the future to give the first dose in every case subcutaneously in order to avoid the mishap.

THE INCREASE IN DOSAGE

The temperature reaction to the preceding dose was the guide used. The only rule applied was not to increase the dosage as long as there was a definite rise of temperature to the former injection, but as far as possible to give doses large enough to produce a febrile reaction. No comparable experiments were made, using minute doses and avoiding febrile reactions. No reaction under 104°F. was considered febrile. The amount of increment of dosage depended on the number of previous inoculations. In general, it was 0.1 cc. with each succeeding dose, but afterward it was 0.3 or even 1.0 cc. as time progressed. The different manner in which individual guinea pigs react and the rate of increment in dosage is shown in charts 1 and 2 and also in table 2. The aim was to reach a final dose of 2 cc. of tuberculin, since this was the amount which, in untreated tuberculous guinea pigs, in every case produced a fatal outcome with characteristic rapid fall in temperature.

THE TIME INTERVAL BETWEEN DOSES

It appeared to us extremely important to determine, if possible, not only the optimum time interval, if such existed, but particularly if some time intervals between doses produced disagreeable results. Accordingly, some animals were given their second dose on the following day and others on the 2nd, 3rd, 4th, 5th and 7th days afterward, respectively (table 2). Only one guinea pig (C-16) reacted unfavorably to the second dose, which was 0.1 cc. repeated subcutaneously *one week* after the first. This animal developed pleural changes and a continuous fever, which lasted three weeks and from which it ultimately recovered. It was also observed that when the interval between first and second dose was long (5–7 days) the increment in dosage was slower. Consequently, 2 or 3 injections a week seemed most advantageous, and during the second, third and fourth weeks this was adhered to.

EVIDENCES OF DESENSITIZATION

The skin test: This did not become negative until 30 days after the initiation of treatment (table 1). At this time all the intravenously inoculated animals were negative to 10 per cent tuberculin and eight of the 10 subcutaneous-group animals. Nine days previously none of the animals gave completely negative test, although the degree of reactivity was, in general, less than encountered with the previous test dose before treatment. The actual amount of tuberculin injected was not the deciding factor (table 2), since one animal, D-1, which received in all only 1.7 cc. of tuberculin in 10 doses over a period of four weeks was negative, while another, C-2, was still somewhat positive after 11 doses, totalling 6 cc., in a period of three weeks. It would thus seem that, as far as the disappearance of a positive tuberculin skin test is concerned, a minimal time interval is necessary (in these experiments 30 days) irre-

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CHART 1

Animal C-2. Illustrates rapid desensitization to subcutaneous inoculation, which also protected against intravenous inoculation. A febrile reaction followed all four doses of 2 cc. The animal finally was skin-test negative to 50 per cent tuberculin.

Animal C-3. Desensitization slower and skin test persisted longer. No lethal shock followed 1 cc. O. T. intravenously.

Animal C-4. Rapid desensitization and no febrile reaction to the last 2 cc. tuberculin intravenously.

Animal C-7. To illustrate a week's interval between the first and second doses. Increment of dosage slow at first, but desensitization accomplished quickly. Skin test still negative three weeks after tuberculin treatment ceased.

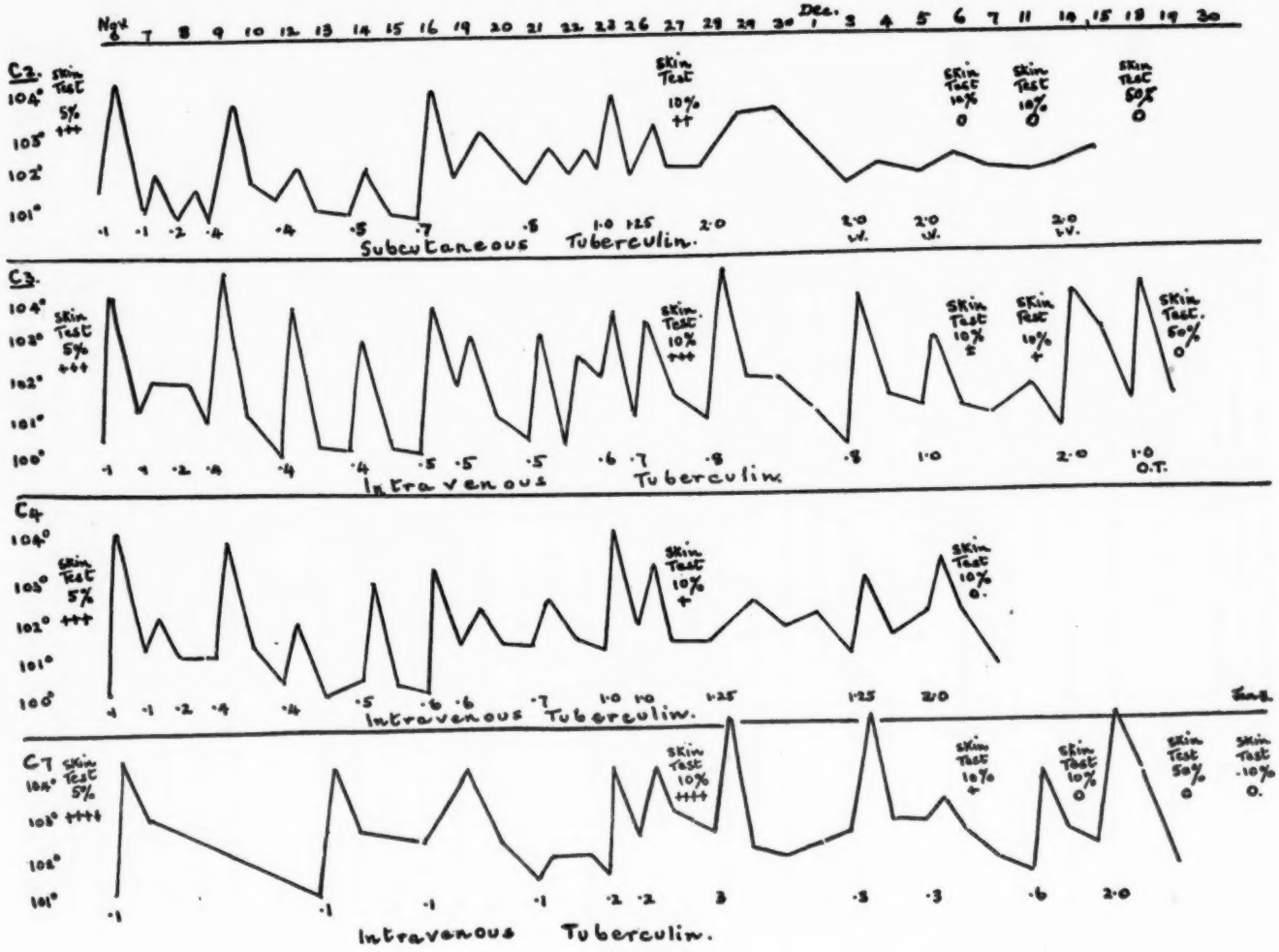
Nov. 6 7 8 9 10 12 13 14 15 16 19 20 21 22 23 26 27 29 29 30 Dec. 1 3 4 5 6 7 11 14 15 18 19 30
C2.
Skin Test 5% +++
Skin Test 10% ++
Skin Test 10% 0
Skin Test 10% 0
Skin Test 50% 0
Subcutaneous Tuberculin.
C3.
Skin Test 5% +++
Skin Test 10% +++
Skin Test 10% ±
Skin Test 10% +
Skin Test 50% 0
O.T.
Intravenous Tuberculin.
C4
Skin Test 5% +++
Skin Test 10% +
Skin Test 10% 0.
Intravenous Tuberculin.
C7
Skin Test 5% ++++
Skin Test 10% ++++
Skin Test 10% +
Skin Test 10% 0
Skin Test 50% 0
Skin Test 10% 0.
Intravenous Tuberculin.

CHART 1

spective, within wide variations, of the quantity of tuberculin injected or the number of reactions produced. Within this minimal time phase, desensitization was accomplished with as little as 1.7 cc., while one animal had had as much as 12 cc. No attempt was made to determine how long the negative skin test would have persisted with or without further treatment. Some of the animals were tested for one month afterward, and most remained negative to 10 per cent and even 50 per cent tuberculin.

The general reaction: A glance at chart 1 shows that the febrile reaction elicited at first with 0.1 cc. of tuberculin given either subcutaneously or intravenously is only produced on succeeding doses with larger amounts of tuberculin. Ultimately no temperature rise occurs after 1.0 to 1.25 cc., but it is only rarely that 2.0 cc. fails to cause an elevation in temperature; but this amount, as stated previously, usually produces a definite rise even in normal guinea pigs. In tuberculous, untreated guinea pigs 2.0 cc. causes a fall of temperature and death, so that the febrile reaction obtained in the treated animals would appear to be evidence of a high degree of desensitization. Only in three animals did a *nonfatal* fall of temperature (see C-13, chart 2) occur after the first 2.0-cc. dose, and in all these animals the increment in dosage had been purposely large (previous dose 0.6 to 0.8 cc.) in order to test the point. These animals were then only partially desensitized. Generally speaking, animals which had been desensitized by the subcutaneous method did not react to the intravenous inoculation. In several, inoculated subcutaneously, the large inflammatory masses which developed at the site of inoculation

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CHART 2

Animal C-16. Continuous fever and pleural changes developing after second dose of tuberculin one week after first dose. No desensitization to skin test.

Animal C-13. To show the nonlethal fall in temperature occurring in a partially desensitized animal after 2 cc. tuberculin intravenously.

Animal C-11. The one tuberculous guinea pig which was shocked after a single dose of 0.1 cc. intravenously.

Animal A-3. The febrile reaction in a tuberculous guinea pig after 1 cc. tuberculin intravenously.

Animal A-7. The characteristic rapid lethal shock occurring in a tuberculous guinea pig after 2.0 cc. tuberculin intravenously.

Animal W-6. The protection of lethal shock of a tuberculous guinea pig by the administration of human serum from convalescent patient with pleurisy with effusion.

Animal E-4. The slight febrile reaction in a normal guinea pig after 2.0 cc. of tuberculin intravenously.

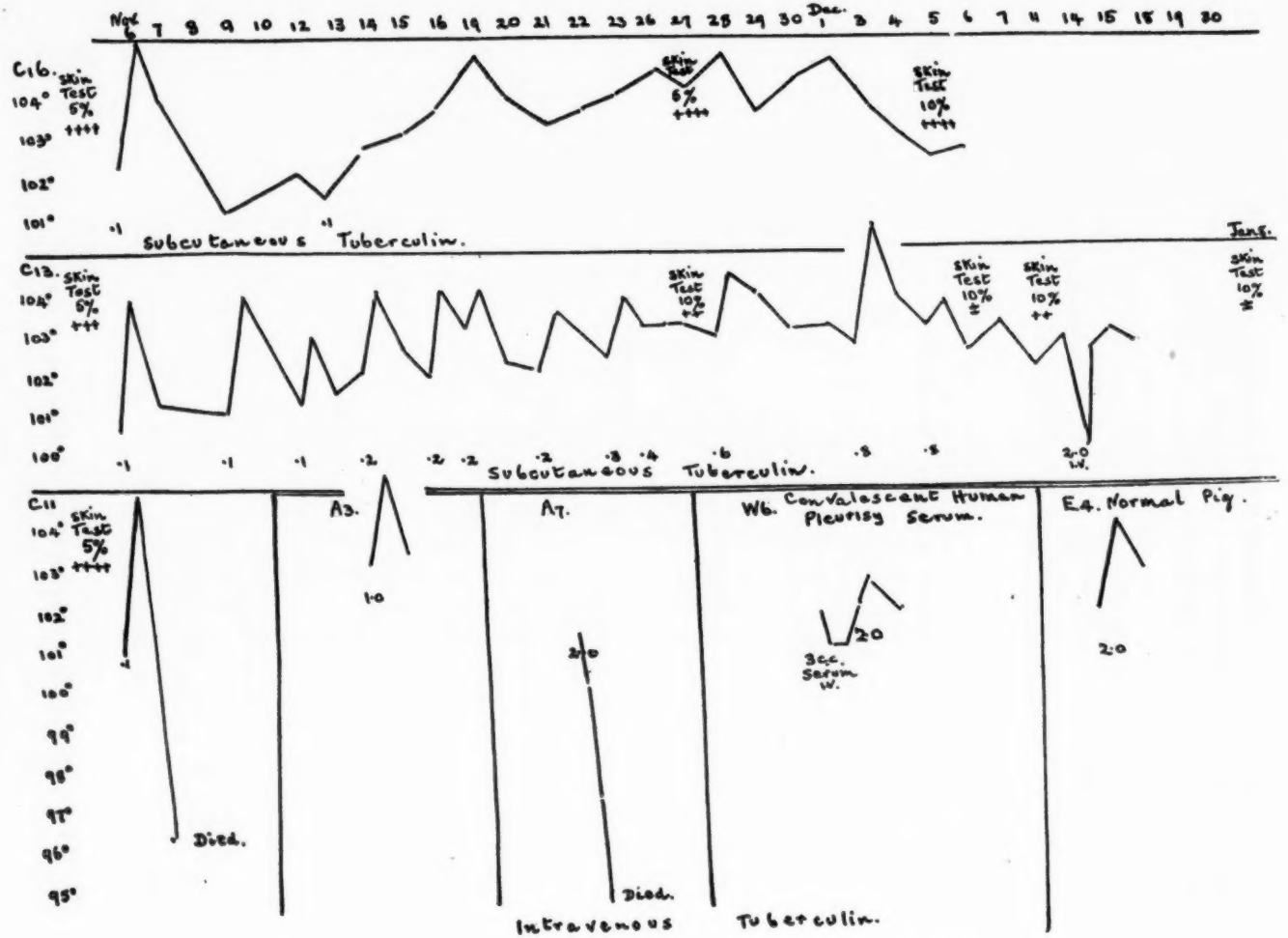
Nov 6 7 8 9 10 12 13 14 15 16 19 20 21 22 23 26 27 28 29 30 Dec. 1 3 4 5 6 7 11 14 15 18 19 30
C16.
Skin Test 5% ++++
Skin Test 5% ++++
Skin Test 10% ++++
Subcutaneous Tuberculin.
C12.
Skin Test 5% +++
Skin Test 10% ++
Skin Test 10% ±
Skin Test 10% ++
Skin Test 10% ±
Jan.
2·0 I.V.
Subcutaneous Tuberculin.
C11
Skin Test 5% ++++
Died.
A3.
1·0
A7.
2·0
Died.
Intravenous Tuberculin.
W6. Convalescent Human Pleurisy Serum.
20
3 c.c. Serum I.V.
E4. Normal Pig.
2·0

CHART 2

TABLE 1

The loss of skin reaction as an indication of desensitization

CONTROLS					TREATED							
Number	Tuberculin			Degree of tuberculosis	Number	Tuberculin						Degree of tuberculosis
	Oct. 29 5%	Dec. 11 1%	Jan. 7 10%			Oct. 29 5%	Nov. 27 10%	Dec. 6 10%	Dec. 11 10%	Dec. 18 50%	Jan. 7 10%	
					Intravenous							
A-1	4	–	–	+	C-3	3	3	0	1	0	–	0
A-3	2	–	–	+	C-4	3	1	0	–	–	–	0
B-4	3	–	–	+	C-7	3	3	0	1	1	–	0
B-5	4	–	–	++	C-8	4	3	0	1	0	–	0
B-6	4	–	4	+++	C-9	3	2	0	0	0	–	0
F-1	4	–	4	+	C-10	4	4	0	1	2	0	++
F-3	4	–	4	+	C-12	3	3	0	–	–	–	+
F-5	4	4	2	+	C-17	4	4	0	0	1	0	0
F-8	4	4	–	+++	D-1	4	4	0	0	2	0	0
F-9	4	4	–	++								
F-10	4	4	–	++	*Subcutaneous*							
F-11	4	3	–	+								
F-12	4	3	1	+	D-2	1	3	0	–	–	–	+
G-1	4	–	4	+	C-1	3	2	1	–	–	–	+
H-1	4	4	–	0	C-2	3	1	0	0	0	–	0
H-2	4	–	–	+++	C-5	3	1	0	–	–	–	+
H-3	4	4	3	+	C-6	3	3	0	0	0	0	0
H-4	2	1	4	+	C-13	3	2	0	2	2	0	+
H-5	1	2	2	+	C-14	4	3	0	–	–	–	+
					C-15	4	4	3	2	1	3	0
					C-18	4	4	0	0	0	0	0
					C-11	Died in shock after first I.V. inoculation of 0.1 cc. tuberculin						+
					C-16	Developed pleural changes and fever for 3 weeks after second subcutaneous inoculation of 0.1 cc. tuberculin, one week after first dose of 0.1 cc. No further treatment						+

Skin Tests

4 = necrotic reaction
3 = erythema with white centre
2 = erythema 1 cm. and over
1 = slight erythema
0 = completely negative

Degree of Tuberculosis

+++ generalized
++ local site and liver and spleen
+ local site and lymph node
0 no gross tuberculosis

were painful complications. Not all animals showed this, and there was no way of predicting those that would. This complication was obviated by the intravenous inoculations. In a few instances, the administration

of 1.0 cc. O.T. (Parke, Davis & Co.) intravenously in completely desensitized guinea pigs failed to cause shock.

TABLE 2

Tolerance to increasing amounts of tuberculin as test of desensitization

(General reaction)

NUMBER	NOV. 6	1ST WEEK		2ND WEEK			3RD WEEK			4TH WEEK		5TH WEEK	6TH WEEK	TOTAL
Intravenous														
														cc.
C-3	.1	.1	.2	.4	.4	.4	.5	.5	.5	.6	.7	.8	.8	1.0	2.0	9.0
C-4	.1	.1	.2	.4	.4	.5	.5	.5	.7	1.0	1.0	1.25	1.25	2.0		9.9
C-7	.1	.1	.3	.3		.3	.4	.4	.4	.5	.7	.8	.8	1.0	2.0	8.1
C-8	.1	.1	.3	.3		.3	.3		.3	.4	.6	.7	.7	.7	2.0	6.8
C-9	.1	.1	.3			.3	.3	.3	.4	.5	.7	.8	.8	1.0	2.0	7.6
C-10	.1	.2	.4			.4	.4	.4	.4	.5		.5	.5	.7	2.0	6.5
C-12	.1	.1				.2	.2	.3	.4	.5	.7	1.0	1.0	1.0		5.5
C-17	.1					.1	.1	.1	.1	.2	.2	.3	.3	.3	.6, 2.0	4.4
D-1	.1	.1				.1	.1	.1	.1	.2	.3	.3	.3			1.7
C-11	.1	Died, tuberculin shock														
Subcutaneous																
C-1	.1	.1	.2	.4	.4	.4	.4	.4	.5	.6	.7	.8	.8	.8		6.6
C-2	.1	.1	.2	.4	.4	.5	.7	.7	.8	1.0	1.25	2.0	2.0 (I.V.)	2.0 (I.V.)	2.0 (I.V.)	14.15
C-5	.1	.1	.3	.3		.4	.5	.5	.5	.7	.7	1.0	1.25	1.25		7.6
C-6	.1	.1	.3	.3		.3	.3	.4	.4	.5	.6	.8	.8	1.0	2.0 (I.V.)	7.9
C-13	.1	.1	.1			.2	.2	.2	.2	.3	.4	.6	.8	.8	2.0 (I.V.)	6.0
C-14	.1	.2	.4			.4	.5	.5	.6	.7	.7	1.0	1.25	1.25		7.6
C-15	.1	.1				.1	.1	.1	.1	.1	.2	.3	.3	.3, .6	2.0 (I.V.)	4.4
C-18	.1					.1	.1	.2	.3	.4	.6	1.0	1.25	2.0	2.0 (I.V.)	7.95
D-2	.1	.1				.1	.1	.1	.2	.4	.7	1.0	1.25			3.85
C-16	.1	Continuous fever and pleural changes for 3 weeks														0.2

I.V. = intravenous.

AUTOPSY FINDINGS

These are listed in table 3. When the experiment was concluded, four months after infection, by killing the surviving animals, there was a noticeable difference in the amount and extent of tuberculosis in the two groups. Of the 19 controls, only one showed no gross tuberculosis at autopsy, and this animal had a chronic inflammation of the middle ear. On the other hand, 11 of the 18 treated animals showed no tuberculosis.

No generalized lesions were found among the treated, while there were 3 controls that showed them. The infecting strain was obviously not highly virulent.

TABLE 3

Autopsy findings

CONTROLS				TREATED				
Number	Days of life	Cause of death	Degree of tuberculosis	Number	Days of life	Cause of death	Last skin test	Degree of tuberculosis
A-1	45	Killed	+	C-1	84	Killed	1	+
B-5	46	Killed	++	C-4	84	Killed	0	0
A-3	49	Pneumonia; peritonitis	+	C-5	84	Killed	0	+
B-4	49	Killed	+	C-12	84	Killed	0	+
H-2	82	Killed	+++	C-14	84	Killed	0	+
F-9	91	Killed	++	D-2	84	Killed	0	+
H-1	92	Killed, otitis	0	C-2	93	Pneumonia	0	0
F-10	92	Killed	++	C-7	104	Peritonitis	1	0
F-8	95	Killed	+++	C-8	108	Pneumonia	0	0
F-11	109	Killed	+	C-3	109	Killed	0	0
H-3	113	Killed	+	C-6	113	Killed	0	0
B-6	113	Killed	+++	C-9	113	Killed	±	0
F-5	116	Killed	+	C-10	113	Killed	±	++
F-12	119	Killed	+	C-13	113	Killed	±	+
H-4	119	Killed	+	C-15	113	Killed	3	0
H-5	119	Killed	+	C-17	113	Killed	0	0
G-1	121	Killed	+	C-18	113	Killed	0	0
F-1	121	Killed	+	D-1	113	Killed	0	0
F-3	121	Killed	+					
				C-11	51	Tuberculin shock	3	+
				C-16	84	Killed Incompletely treated	4	+

WEIGHT CURVES

Unfortunately, regular weights were not taken, but the only animals which became emaciated were those receiving at the completion of the desensitization several further doses of 2 cc. No deaths other than the two previously mentioned could be directly attributed to the treatment.

WILL THE SERUM OF DESENSITIZED ANIMALS PROTECT OTHER TUBERCULOUS ANIMALS FROM LETHAL TUBERCULIN SHOCK?

In a comparatively small number of rather desultory experiments we were unable to show any protection against 2 cc. of tuberculin intra-

venously in tuberculous guinea pigs. A single observation, however, appears unusual enough to warrant mention. A human serum obtained from Dr. H. S. Willis from a late convalescent patient with pleurisy with effusion did protect a tuberculous guinea pig in a 3-cc. dose against 2 cc. of tuberculin given intravenously the following day. (See chart 2, animal W-6.) The future course of this animal was also interesting. The skin test, which was strongly positive before, was negative four days afterward and again a week later. At this point another 2 cc. of tuberculin was given intravenously, but without febrile response. The skin test was again negative two weeks later, but the following week it was strongly positive once more, and at the conclusion of the experiment generalized tuberculosis was found at autopsy.

IS THERE A CAUSAL RELATIONSHIP BETWEEN DESENSITIZATION AND IMMUNITY?

Continued treatment of tuberculous guinea pigs with unheated synthetic-medium tuberculin, either subcutaneously or intravenously, has resulted in the treated animals becoming desensitized to both the skin test and the general reaction. This has been accompanied by the localization and healing of their tuberculous lesions. Is one therefore justified in assuming that these two are causally related? If one were using a single chemical substance, such an assumption would seem justifiable, but the tuberculin used here is undoubtedly a complex mixture of numerous substances; and may one not with equal justification argue that the substances which produced the desensitization are not necessarily the same as those which produced the immunity? One would at any rate prefer to leave the question of cause and effect open until he had used, as far as possible, single chemical constituents of the original tuberculin.

SUMMARY AND CONCLUSIONS

1. The unheated Long synthetic-medium "tuberculin" used in these experiments has in every instance killed allergic tuberculous guinea pigs in doses of 2 cc. intravenously, the animals showing the characteristic fall in temperature. A like dose in normal guinea pigs usually causes a moderate febrile reaction.

2. Smaller doses, 0.1 to 1.0 cc., administered either intravenously or subcutaneously, produce a febrile reaction in tuberculous guinea pigs, the temperature reaching its peak in three to seven hours and returning to

normal in 24 hours. Occasionally these doses cause lethal shock or a continued fever associated with serous effusions.

3. By a gradual increment in dosage, at intervals of 2 or 3 days, when the previous dose has failed to elicit a febrile reaction, a point is reached in about 30 days, where, after 8 to 10 doses totalling 2.5 to 5 cc. of tuberculin, 1 cc. fails to give a febrile reaction. After further treatment, 2 cc. fails to produce lethal shock. Such animals, completely desensitized against a general tuberculin reaction, also fail to show a positive skin test with 10 per cent and in some instances 50 per cent tuberculin.

4. A too-long interval between doses and a too-large increment may be dangerous, and the actual amount of tuberculin necessary to produce desensitization is very variable. A certain period of time must elapse, during which a number of reacting doses is given before desensitization can be anticipated.

5. When killed and autopsied, the desensitized animals were found to show markedly less tuberculosis than the controls. No causal relationship has been proved, however, since the complex nature of the material used does not allow one to state that the substance which causes the desensitization is the one responsible for the immunity, and the two may or may not be related.

6. The favorable results obtained in our experiments are due, in our opinion, not only to the type of antigen used but also to the fact that the infecting strain was of low virulence and the increment in dosage of the tuberculin was not a standard procedure but depended on each individual animal's reaction to its former injection.

7. Normal or tuberculous guinea pig serum and the serum from some of the desensitized animals have not protected tuberculous pigs from lethal tuberculin shock. One human serum from a convalescent case of pleurisy with effusion did protect, but no others were tried.

8. The intravenous route has one advantage over the subcutaneous; namely, that large local inflammatory reactions sometimes seen after subcutaneous inoculation are avoided. The initial intravenous dose should, however, be smaller than used here, since one animal died after a first intravenous inoculation of 0.1 cc.

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EXPERIMENTAL TUBERCULOUS INFECTION IN THE GUINEA-PIG FOETUS COMPARED WITH THAT IN THE ADULT[1,2]

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Extensive investigations of tubercle bacilli in artificial culture on laboratory media have demonstrated that the growth characteristics, the chemistry and the virulence of the microörganisms are largely dependent on the constituents of the medium and the environment to which they are exposed. On some media the organisms die. On others they grow abundantly, but with marked difference in their colony morphology and definite alteration in their virulence. Considering these observations, it seems reasonable to assume that differences in the tissue medium and environment within infected individuals and animals may be responsible for the wide variations in native resistance to the microörganisms. Native resistance is particularly mentioned, for this report seeks to avoid acquired resistance in which immunity factors, as contributed by first infection, are at play.

In considering native resistance, it is a recognized clinical observation that there is a marked difference in the response of various individuals to first infection with the tubercle bacillus. The majority overcome that infection and completely abort it, leaving as residuum a fibrous or a calcified focus. Others, under similar conditions of exposure and environment, succumb to the infection and eventually become tuberculous. Experimentally, too, there is wide variation in the response of different species of animals to the same type of organisms (1). Some react very sluggishly or not at all. Others develop far-advanced disease in a comparatively short time. Such action is usually attributed to a native susceptibility or insusceptibility of the host to the tubercle bacillus. Hereditary influences and possible changes in the biological and biochemical tissue constituents of the host are often referred to.

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York. This work was done in part at Cambridge University, Cambridge, England, under a grant from the National Research Council.

[2] Presented at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

Tangible facts for this difference in response are, however, largely lacking.

There is experimental evidence that changes of a tissue medium *in vivo*, comparable to changes of an artificial medium *in vitro*, influence the growth and multiplication of the tubercle bacillus. The evaluation of such an influence in the animal body, however, is rather indirect. The extent and character of the disease process must give evidence of conditions that are favorable or unfavorable to the inoculated bacilli, for it is still debatable whether the typical acid-fast phase of the microorganism is the only form in which it occurs. In some lesions, direct observation of stainable bacilli may give an indication of the ability of that animal's tissues to combat the organisms. The bacilli may be well stained, numerous and often grouped, but in other lesions they may be poorly stained, few in number and well isolated. In still others they may be absent. Such observations may have a definite relation to the lesion in question. On the whole, however, they are by themselves quite unreliable in determining the activity or inactivity of a lesion, the susceptibility or insusceptibility of an individual host.

Regarding changes in the media: Glycerol, a growth-promoting substance in artificial culture of the tubercle bacillus, has been shown to influence the rate and spread of tuberculosis in the animal body (2). Glycerol fed or injected over long periods of time to tuberculous rats, animals ordinarily subject to a slowly progressive tuberculosis (1), appears definitely to enhance the growth of the tubercle bacilli in the lesions and increase the extent of the disease. Palmitic acid, fed to tuberculous guinea pigs, in the hope of forcing the synthesis of free glycerol into neutral fat and so decrease the amount in the tissues, retards the development and spread of the tuberculosis.

The predilection of the tubercle bacillus for certain tissues has been attributed to the nitrogen which those tissues make available for growth of the microörganism (3). This view, however, has been questioned. It is held that the nonprotein nitrogen in the fluids of the body adequately meet the growth requirements of the tubercle bacillus.

Further, there is substantial experimental evidence that a definite relation exists between the oxygen supply and the velocity of growth of the tubercle bacillus (4) (5) (6). To such a relationship has been ascribed the varying susceptibility of different organs to tuberculosis (7) (8). The beneficial effect of lung collapse on pulmonary tuberculosis has been associated with a decrease in oxygen and an increase in carbon dioxide in the atelectatic tissue (9).

These observations are significant enough to warrant further study of the influence of radical changes in living tissues upon the growth of tubercle bacilli and upon the extent and character of the disease process which they produce. It is difficult to alter the tissue pabulum radically by experimental methods and still preserve conditions necessary for life. The tissue of the living foetus *in utero*, however, presents a chemical environment and a metabolic activity that is radically different from that in the animal after birth. Such tissue might very well influence the growth of microörganisms and the disease process which they produce. Guinea-pig foetuses were therefore infected with human-type tubercle bacilli, and their tissue response was compared with those in adult control pigs infected with the same organisms.

METHODS

Human-type tubercle bacilli M684 and H63,[3] maintained on egg media and of cultural age of from 17 to 20 days, were used throughout the experiment as the infecting organisms. An amount calculated on the basis of dry weight was triturated in a glass mortar and suspended in saline solutions. In one series of animals black india ink was added to the suspension in order to mark the site of inoculation.

Inoculations were made as follows: Foetal guinea pigs, ranging in age from 40 to 50 days, were approached by a laparotomy incision under general anaesthesia. On exposing the pregnant uterus the foetuses were easily visible, and by gentle manipulation could be brought in close proximity to the uterine wall. Through a tuberculin syringe and a 27-gauge needle, subcutaneous or intraperitoneal inoculations of the foetuses were readily administered. Usually only one foetus was injected. In a few cases, depending upon the facility of approach, two of them were inoculated. The injection caused no appreciable haemorrhage, and abortion at this age period did not necessarily follow. The maternal abdomen was closed by suture and the pregnancy was allowed to progress to term. As controls, adult guinea pigs were infected at the same time intraperitoneally or subcutaneously with an equal amount of the same suspension.

The animals were killed at varying intervals after infection, usually

[3] M684: Isolated by Dr. Stanley Griffith from a case of tuberculous meningitis in a child, and proved to be fully virulent for guinea pigs.

H63: Saranac Laboratory strain, isolated from a case of adult tuberculosis, and fully virulent for guinea pigs.

at birth of the foetus. Paraffine sections were routinely made from the lungs, liver, spleen, lymph nodes and the maternal uterus. They were stained with haematoxylin-eosin and, in addition, all sections of splenic tissue were treated by the Ziehl-Neelsen method (Hopkins's modification) for the demonstration of tubercle bacilli.

As a basis of comparing the extent of the tissue response in the intrauterine-infected guinea pigs and their respective control adult guinea pigs, the average diameter was taken of the largest tubercles observed microscopically in the spleen and in the liver of each animal. The measurements appear in the chart as the diameters of representative tubercles drawn to a scale of 50 micromillimetres to 1 millimetre. The character of the disease process was largely determined by microscopic observation of the type of cell, the amount of necrosis, and the number of acid-fast bacilli in the lesions as presented by the various animals.

The guinea pigs included in the present report will be considered in two groups, with subdivisions into series consisting of the maternal guinea pig, the foetus and the adult infected control animal. Group 1 comprises a series of animals that were killed at or near birth of the foetus from 9 to 25 days after infection. Group 2 is based upon offspring that were allowed to live some days after birth, to ascertain the amount of tuberculosis that would ultimately develop.

Group 1

Series 1: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.2 mgm. H63 tubercle bacilli in 0.2 cc. saline solution. The maternal guinea pig was found dead 9 days later. The dead foetus was removed by caesarian section and the control animal was likewise killed 9 days after infection.

Maternal guinea pig: Peritonitis secondary to infection in the abdominal incision. No gross or microscopic evidence of tuberculosis.
Foetal guinea pig: The tissues were in good state of preservation but showed no definite evidence of tuberculosis. Tubercle bacilli not found.
Control guinea pig: The omentum was contracted about the stomach. It was firm and infiltrated with scattered large mononuclear cells and lymphocytes without definite tubercle formation. The spleen showed occasional small mononuclear cell tubercles confined to the malphigian corpuscles. Bacilli were found with difficulty. The liver, abdominal lymph nodes and lungs were negative for tubercle.

Series 2: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.1 mgm. H63 tubercle bacilli in 0.2 cc. saline solution. The maternal guinea pig was found dead 10 days later. The foetus was removed by caesarian section, and the control animal was likewise killed 10 days after infection.

Maternal guinea pig: Findings similar to those in series 1.
Foetal guinea pig: No gross or microscopic tuberculosis. Tubercle bacilli not found.
Control guinea pig: Except for slightly larger tubercles in the spleen and for a few intrapulmonic aggregates of mononuclear cells and lymphocytes (probably early tubercles) in the lungs, the observations were similar to those made in series 1.

Series 3: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.1 mgm. H63 tubercle bacilli in 0.2 cc. saline solution and killed on the date of foetal delivery by caesarian section 12 days after infection.

Maternal guinea pig: Definite lesions of tuberculosis were not found.
Foetal guinea pig: Tuberculosis was not found. Tubercle bacilli absent.
Control guinea pig: The omentum was contracted about the stomach. The spleen, liver and abdominal lymph nodes presented numerous mononuclear cell tubercles, many with diffuse polymorphonuclear leucocytic infiltration or small central foci of necrosis. Few deeply stained, short, isolated bacilli were found in the splenic lesions. The lungs showed no disease.

Series 4: Three foetuses and one adult control guinea pig were inoculated intraperitoneally with 0.2 mgm. M684 tubercle bacilli in 0.2 cc. saline solution, and killed on the date of foetal birth 16 days after infection.

Maternal guinea pig: In the wall of the left uterine horn, presumably at the site of puncture, there was a small mononuclear-cell tubercle. There was no other evidence of tuberculosis.
Foetal guinea pig A: Gross or microscopic tubercles were not observed. Tubercle bacilli were not found.
Foetal guinea pigs B and C: One microscopic tubercle was found in the spleen of B and two in that of C. The tubercles were made up of mononuclear cells. Polymorphonuclear leucocytic infiltration or necrosis was not evident. A very occasional deeply stained, short bacillus was found. In the liver the tubercles were poorly defined and composed of mononuclear cells. The lungs showed no disease.

Control guinea pig: The site of the needle track in the abdominal wall presented a small caseous lesion. Extensive abdominal tuberculosis was present. The splenic tubercles were epithelioid in character with little polymorphonuclear leucocytic infiltration and small points of central necrosis. Tubercle bacilli were numerous, deeply stained, elongated and beaded. The liver tubercles showed small central foci of necrosis. The abdominal lymph nodes were largely caseous. The lungs presented small loose aggregations of lymphocytes and a few polymorphonuclear leucocytes, probably early tubercles.

Series 5: The foetus and an adult control guinea pig were inoculated subcutaneously with 0.2 mgm. H63 tubercle bacilli in 0.2 cc. of a saline solution containing india ink. The animals were killed on the date of foetal birth 17 days after infection.

Maternal guinea pig: In the wall of the right uterine horn there was a localized focus of mononuclear cells, probably early tubercle-formation. The spleen and lungs contained microscopic tubercles with diffuse polymorphonuclear leucocytic infiltration and central points of necrosis. The liver was negative.
Foetal guinea pig: There was a black nonulcerated subcutaneous lesion, 3 x 4 mm. at the site of injection. Gross visceral tuberculosis was not observed. The subcutaneous lesion was a definitely localized collection of large mononuclear cells and polymorphonuclear leucocytes with a peripheral ring of carbon-filled phagocytes. It was enclosed by a fibrous and hyalinized wall with little extension into the surrounding tissue (figure 1). Bacilli were easily found, usually intracellular and chiefly confined to dust-filled mononuclear cells and polymorphonuclear leucocytes. The spleen, liver, abdominal lymph nodes and lung revealed no microscopic evidence of tubercle. Acid-fast bacilli were not found.
Control guinea pig: Black subcutaneous ulcerated lesion, 1 x 2 cm., at the site of injection. Gross tuberculosis observed in the spleen and liver. The subcutaneous lesion was largely composed of polymorphonuclear leucocytes, with a thick peripheral zone of mononuclear and epithelioid cells. The tuberculous process extended into the surrounding tissue, with the formation of thick cellular bands and discrete epithelioid tubercles. Carbon pigment was diffusely scattered throughout the lesion (figure 2). Acid-fast bacilli were more numerous than in the foetal lesion. They were generally well stained, elongated, beaded and often seen in groups. The spleen contained large mononuclear-cell tubercles some with central polymorphonuclear leucocytic infiltration. The liver revealed small epithelioid tubercles many with central points of necrosis. The abdominal lymph nodes were largely replaced by discrete and conglomerate epithelioid tubercles with central foci of polymorphonuclear leucocytes or necrosis. The lungs presented an occasional small tubercle of mononuclear cells and lymphocytes.

Series 6: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.2 mgm. H63 tubercle bacilli in 0.2 cc. saline solution and killed on the date of foetal birth 18 days after infection.

Maternal guinea pig: The uterine wall showed an occasional small focus of large mononuclear cells and few polymorphonuclear leucocytes, but no definite tubercle-formation. The spleen contained a few small epithelioid tubercles confined to the malphigian corpuscles. The liver, abdominal lymph nodes and lungs were negative.
Foetal guinea pig: There was no gross tuberculosis. Tubercle bacilli were not obtained in culture of abdominal washings. The spleen contained small epithelioid tubercles without polymorphonuclear leucocytic infiltration in such lesions. The liver showed a very occasional leucocytic infiltration. The abdominal lymph nodes were moderately enlarged, but definite tubercle-formation was not observed. The lungs contained tubercles of large mononuclear cells.
Control guinea pig: Extensive gross tuberculosis. The spleen was studded with conglomerate tubercles that contained necrosis. Tubercle bacilli were numerous, well stained, elongated and isolated. The liver showed epithelioid tubercles with small central areas of necrosis. The abdominal and retrosternal lymph nodes were caseous. The lungs contained small compact aggregates of mononuclear cells with few polymorphonuclear leucocytes.

Series 7: The foetus and an adult control guinea pig were inoculated subcutaneously with 0.5 mgm. M684 tubercle bacilli in 0.2 cc. saline solution and killed on the date of foetal birth 20 days after infection.

Maternal guinea pig: There was no gross or microscopic evidence of tuberculosis.
Foetal guinea pig: The site of subcutaneous injection was not found. Gross tuberculosis was not evident. The spleen contained a few epithelioid tubercles without polymorphonuclear leucocytic infiltration. An occasional tubercle showed a minute central focus of necrosis. Bacilli were moderately numerous, well stained, elongated and beaded. The liver contained small epithelioid tubercles, many with central points of caseation necrosis. The lungs presented a few loose epithelioid tubercles.
Control guinea pig: The site of subcutaneous injection was ulcerated. The lymph nodes in the adjacent groin were caseous. Abdominal tuberculosis was marked. The spleen contained large conglomerate tubercles, many with centres of polymorphonuclear leucocytes. Tubercle bacilli were numerous and deeply acid-fast. The liver showed a few small tubercles of epithelioid cells. The abdominal and tracheobronchial lymph nodes were caseous, and

contained large accumulations of polymorphonuclear leucocytes. The lungs presented a few small tubercles, loose in structure, composed of mononuclear cells and lymphocytes.

Series 8: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.1 mgm. H63 tubercle bacilli in 0.2 cc. saline solution. The foetus was born 21 days after injection. A tuberculin test of foetus was negative. The animals were killed 23 days after infection.

Maternal guinea pig: The spleen, liver and lungs showed a few small epithelioid tubercles without polymorphonuclear leucocytic infiltration or necrosis.
Offspring: There was no gross evidence of tuberculosis. The spleen showed numerous epithelioid tubercles without central necrosis or polymorphonuclear leucocytic infiltration. Acid-fast bacilli were few: only one was found after examination of five different lesions. The liver contained many small epithelioid tubercles, an occasional one with a minute central focus of necrosis. The lungs presented a few epithelioid tubercles, without necrosis or polymorphonuclear leucocytic infiltration.
Control guinea pig: Extensive gross tuberculosis. The spleen showed large conglomerate tubercles with coalesced centres of polymorphonuclear leucocytes. Tubercle bacilli were very numerous, deeply acid-fast, elongated and beaded. Many branched forms were observed. The liver was studded with epithelioid tubercles, the majority with small central foci of necrosis. The abdominal lymph nodes were largely tuberculous, with extensive polymorphonuclear leucocytic infiltration or caseation. The lungs presented a few epithelioid tubercles.

Series 9: The foetus and an adult control guinea pig were inoculated intraperitoneally with 0.2 mgm. H63 tubercle bacilli in 0.2 cc. saline solution and killed on the date of foetal birth, 23 days after infection.

Maternal guinea pig: The uterine wall showed an occasional microscopic focus of inflammatory cells without definite tubercle-formation. The malphigian corpuscles of the spleen were hyperplastic, diffusely infiltrated with polymorphonuclear leucocytes, and contained small foci of epithelioid cells. The liver presented a very occasional small epithelioid tubercle. The abdominal lymph nodes were tuberculous, and showed marked polymorphonuclear leucocytic infiltration and caseation necrosis. The lungs contained numerous small aggregates of lymphocytes and a few mononuclear cells.
Foetal guinea pig: No gross tuberculosis. The spleen showed numerous epi-

thelioid tubercles without polymorphonuclear leucocytic response or central necrosis. Acid-fast bacilli were numerous, well stained and elongated. The liver contained many epithelioid tubercles without necrosis. The abdominal lymph nodes were negative. The lungs presented numerous small aggregates of large mononuclear cells, lymphocytes and a few small polymorphonuclear leucocytes.

Control guinea pig: Extensive gross tuberculosis. The spleen showed numerous epithelioid tubercles, many with large central accumulations of polymorphonuclear leucocytes and small foci of central necrosis. Tubercle bacilli were found with difficulty. They usually appeared as deeply stained short rods. The liver contained many epithelioid tubercles with diffuse polymorphonuclear leucocytic infiltration. The abdominal lymph nodes were tuberculous. Polymorphonuclear leucocytic infiltration was pronounced. The lungs presented a few small tubercles of mononuclear cells and lymphocytes.

Series 10: Twin foetuses and two adult control guinea pigs were inoculated intraperitoneally with 0.5 mgm. H63 tubercle bacilli in 0.2 cc. saline solution and killed on the date of foetal birth, 25 days after infection.

Maternal guinea pig: The uterine wall showed one small aggregate of lymphocytes and a few large mononuclear cells, probably early tubercle-formation. Numerous epithelioid tubercles were observed in the spleen, many with large central foci of polymorphonuclear leucocytes or caseation necrosis. The liver contained a few epithelioid tubercles, some of which showed central necrosis. The abdominal lymph nodes were tuberculous, with large central accumulations of polymorphonuclear leucocytes.

Foetal guinea pig A: Gross tuberculosis was observed only in the spleen. The tubercles were widely scattered, and epithelioid in character without polymorphonuclear leucocytic infiltration or necrosis (figure 3). A few well-isolated, short and long acid-fast bacilli were found in each lesion. The liver showed small epithelioid tubercles with outlying rings of lymphocytes. A very occasional one revealed minute central foci of necrosis (figure 5). The lungs contained small aggregates of large mononuclear cells with a few lymphocytes and a very occasional polymorphonuclear leucocyte, probably early tubercles. (Guinea pigs and culture-tubes, subinoculated with abdominal washings, became positive.)

Foetal guinea pig B: There was no gross or microscopic evidence of tuberculosis. Acid-fast bacilli were not found. Guinea pigs and culture-tubes, subinoculated with abdominal washings, remained negative.

Control guinea pig: Advanced generalized tuberculosis. The spleen showed

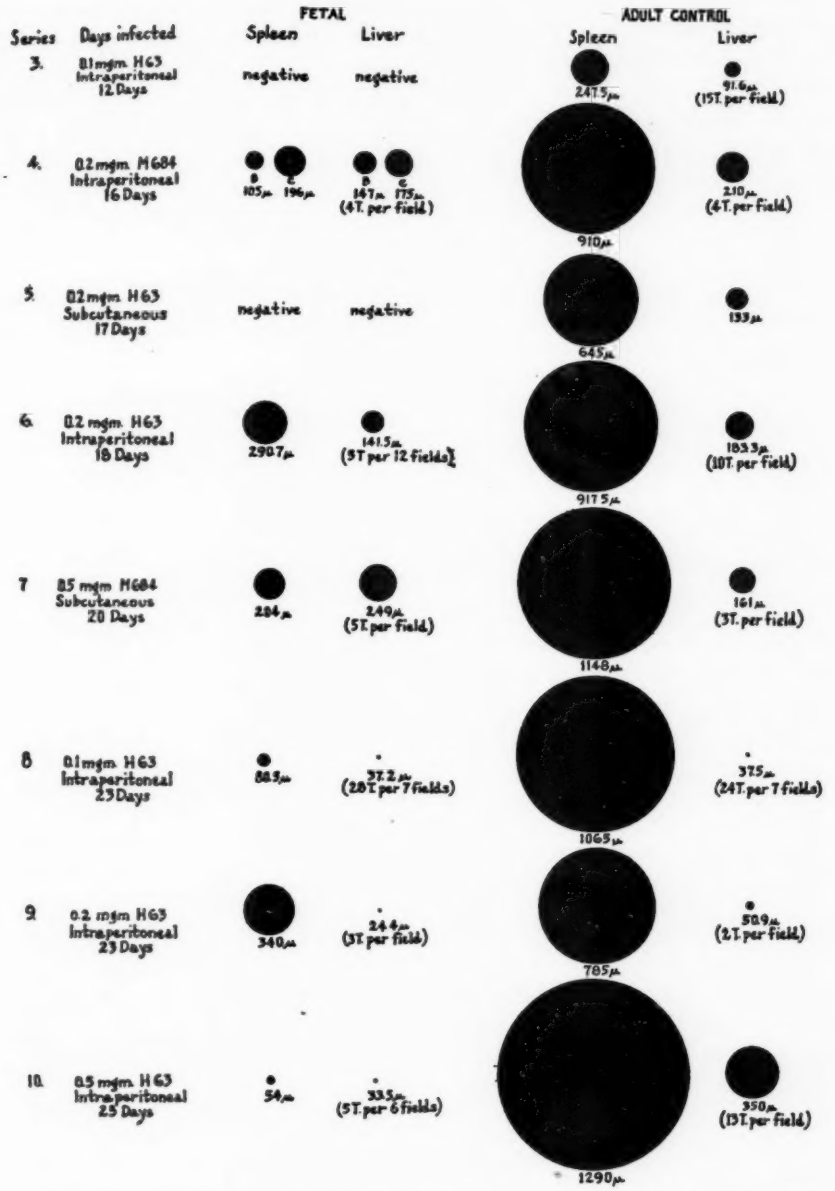


CHART 1. Extent of tuberculosis in the spleen and liver of foetal and adult guinea pigs. Average diameter of representative tubercles drawn to a scale of 50 micro millimeters to 1 millimeter.

conglomerate tubercles with large coalesced centres of polymorphonuclear leucocytes (figure 4). Tubercle bacilli were numerous in all lesions. The liver was studded with epithelioid tubercles, many with central areas of necrosis (figure 6). The abdominal lymph nodes were largely replaced by conglomerate tubercles with large central zones of polymorphonuclear leucocytes. The lungs showed numerous minute epithelioid tubercles with diffuse polymorphonuclear leucocytic infiltration.

Group 2

The offspring in this group were allowed to live after birth to ascertain the amount of tuberculosis that would ultimately develop subsequent to intra-uterine inoculation.

Fig. 1. Section from the subcutaneous lesion of the foetal guinea pig in series 5 inoculated with 0.2 mgm. H63 and killed on date of birth 17 days after infection. Note the localized lesion enclosed by a fibrous and hyalinized wall and with little extension into the surrounding tissue. ×6.5

Fig. 2. Section from the subcutaneous lesion of the adult guinea pig in series 5, inoculated with 0.2 mgm. H63 and killed 17 days after infection. Compare the lesion with that in fig. 1 and note its increased size, the absence of a limiting wall and the extension into the surrounding tissue. ×6.5

Fig. 3. Section from spleen of the foetal guinea pig in series 10, inoculated intraperitoneally with 0.5 mgm. H63 and killed on date of birth 25 days after infection. Note the small, barely visible mononuclear cell tubercle without polymorphonuclear leucocytic infiltration. ×45

Fig. 4. Section from spleen of the adult guinea pig in series 10, inoculated intraperitoneally with 0.5 mgm. H63 and killed 25 days after infection. Compare the tubercle with that in fig. 3. Note its increased size and the large central accumulation of polymorphonuclear leucocytes. ×45

Fig. 5. Section from liver of the foetus shown in fig. 3. Note the two isolated tubercles, one (A) composed of large mononuclear cells and lymphocytes, the other (B) of large mononuclear cells and a small central focus of necrosis. ×87.5

Fig. 6. Section from liver of the adult animal as shown in fig. 4. Compare the size of the tubercle with that in fig. 5 and note the large central area of necrosis at N. ×87.5

Series 11: One foetus and an adult control guinea pig were inoculated intraperitoneally with 0.5 mgm. M684 tubercle bacilli in 0.2 cc. saline solution and killed 11 days after birth of the foetus or 20 days after infection.

Maternal guinea pig: Marked abdominal and thoracic tuberculosis. The type of cellular response was similar to that found in the control animal.
Offspring: Gross abdominal tuberculosis was observed in the spleen and liver. The tubercles in the spleen were of good size, often conglomerate, and epithelioid in character with peripheral rings of lymphocytes and mononuclear

Fig. 1

Fig. 2

Fig. 3

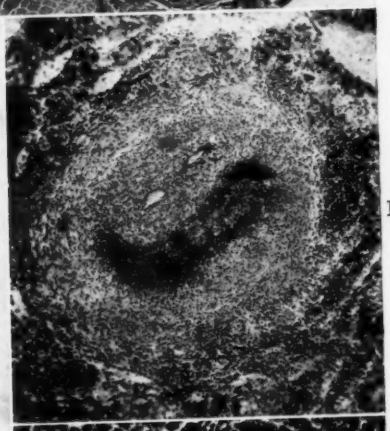
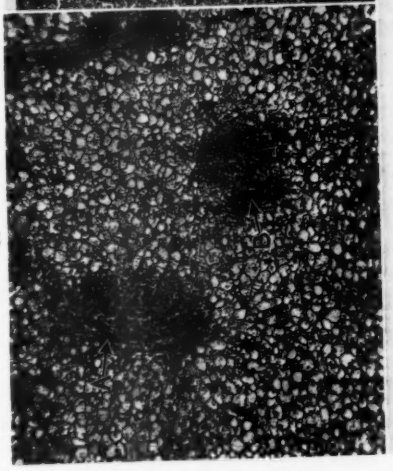


Fig. 4

Fig. 5



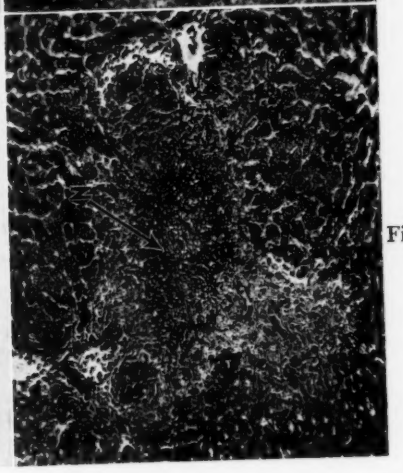


Fig. 6

cells. Polymorphonuclear leucocytic infiltration and central caseation were present but not pronounced. Acid-fast bacilli were found with difficulty. The liver was studded with numerous small tubercles, many with slight diffuse polymorphonuclear leucocytic infiltration and small central foci of necrosis. The lungs contained an occasional eipthelioid tubercle and large areas of diffuse mononuclear-cell infiltration.

Control guinea pig: Extensive gross tuberculosis. The spleen showed numerous conglomerate epithelioid tubercles, many with diffuse polymorphonuclear leucocytic infiltration. A few contained central clusters of polymorphonuclear leucocytes or small foci of necrosis. Numerous elongated and isolated acid-fast bacilli were found. The liver was studded with epithelioid tubercles similar in character to those in the offspring. The abdominal lymph nodes were largely tuberculous, with marked polymorphonuclear leucocytic infiltration. The lungs presented a very occasional small epithelioid tubercle.

Series 12: One of three foetuses was inoculated intraperitoneally with 0.5 mgm. M684 in 0.2 cc. saline solution.

Maternal guinea pig: Died 24 days after birth of the foetuses, or 36 days after infection. Extensive tuberculosis with pronounced caseation and polymorphonuclear leucocytic response was observed in the uterus, spleen, liver, abdominal lymph nodes and lungs.

Offspring A: Died 15 days after death of the maternal guinea pig, 39 days after birth or 51 days after infection. The left cephalic lung lobe showed pneumonic consolidation. Gross tuberculosis was not observed. Microscopically, the responses were primarily epithelioid in character, with diffuse polymorphonuclear leucocytic infiltration of the lesions. Tubercle bacilli were numerous, deeply acid-fast, beaded and elongated.

Offspring B: Died 49 days after the death of the mother, 73 days after birth or 85 days after infection. Gross tuberculosis was observed in the spleen and lungs. Microscopically, the tubercles were largely epithelioid in type, with diffuse polymorphonuclear leucocytic infiltration and caseation. Bacilli were numerous in all lesions.

Offspring C: Killed 122 days after death of the maternal pig, 146 days after birth or 158 days after infection. Gross tuberculosis was evident in all organs. Polymorphonuclear leucocytic infiltration and caseation necrosis were pronounced. Bacilli were numerous and deeply stained.

DISCUSSION

The consistent differences between the extent and character of the response of foetal tissue and that of adult guinea pigs (*cf.* group 1) to inoculated tubercle bacilli indicate that foetal tissue *in utero* is un-

favorable for the growth of the tubercle bacillus and that it retards the development of a tuberculous process. After birth (*cf.* group 2), however, a rather rapid change in the tissue condition occurs that provides a more suitable pabulum for the organisms and permits the development of progressive fatal disease. A discussion of the intrafoetal factors responsible for this adverse influence must at best be only speculative.

Differences in the conditions of the foetus and those in the adult are not sufficiently understood to explain the observed variation in the evolution of tuberculous infection. Many possibilities come to mind that may have some bearing, but so little is known about them that they can only be enumerated. Among them may be mentioned the circulation of blood and lymph, the preponderance of lymphoid tissue and lymphocytosis, the state of the haemoglobin, the rapidity of tissue proliferation and the presence of hypothetical antibodies that must disappear at birth. The chemical composition of the foetal tissues, the high content of vitamine C and the hydrogen-ion concentration are perhaps more likely to influence infection. Restricted physiological activity in the adult is known to favor localization of infection, but at the same time it permits healing to occur more rapidly in a part at rest. Whether the difference in activity and metabolism of the foetal tissues, as compared with the adult, plays any rôle in checking the spread of a tuberculous infection is purely conjectural at the present time. The only factor upon which one is now entitled to speculate intelligently is the oxygen-carbon-dioxide tension in the foetal tissues.

It has been shown (10) (11) (12) (13) (14) that the blood entering the foetus is highly unsaturated with oxygen. As the foetus matures, its oxygen supply relatively decreases so that ultimately the supply becomes quite disproportionate to the demand (11). At term the foetus is definitely cyanotic (13). The experimental data supporting these views were obtained by Eastman in a study of the blood from the umbilical vessels of human babies delivered either normally or by caesarean section; and by Barcroft from a large number of determinations made on pregnant goats and rabbits. The following figures indicate that the guinea-pig foetus suffers a similar oxygen deficiency:[4]
(1) the oxygen content of foetal heart blood is 8.2 volumes per cent;
(2) the oxygen capacity of foetal heart blood is 16.77 volumes per cent;

[4] For these determinations the writer is indebted to Dr. J. Barcroft and E. McCarthy of the physiological laboratory at Cambridge, England.

and (3) the oxygen saturation of blood leaving the foetal heart is 48.9 per cent.

Such oxygen deficiency in the tissues is comparable to that which has been produced *in vitro* for influencing the growth of tubercle bacilli. In one case the oxygen is in the blood-stream, in the other it is in the air surrounding the culture medium. There is positive evidence that a decrease in oxygen and an increase in carbon-dioxide tensions are detrimental to tubercle bacilli growing on an artificial medium (4) (5) (6). There is reason to suppose that the same effect will be exerted on cultures planted in a medium of living tissue. A debatable point in this supposition, however, is whether the modifications in concentration are of sufficient intensity to be inimical to the growth of the tubercle bacillus, but still adequate to support life and rapid growth of the foetal tissue.

It is not the object of this report to definitely affirm this possibly too theoretical a view, but only to suggest it as one factor that may account for the relative resistance of the foetus *in utero* to tubercle bacillus infection.

SUMMARY

Group 1: The response of guinea-pig foetuses to inoculated tubercle bacilli was different from that in adult control guinea pigs both in extent and in character of the reaction.

The foetuses, except for series 5 and 10 (A), failed to reveal gross evidence of tuberculosis. In four cases, series 1, 2, 3, and 10 (B) even microscopic tubercles were not found. In the foetuses with disease the splenic tubercles were strikingly smaller than those in the adult control animals (*cf.* chart 1). This dissimilarity in size was not so obvious between the hepatic tubercles present in foetuses and those in the adult guinea pigs. In the adult animals, however, they were often more numerous.

The response in the foetuses was primarily mononuclear or epithelioid in character. Polymorphonuclear leucocytic infiltration or necrosis were never prominent features. In the adult control guinea pigs, however, tuberculosis was generally well advanced, with conspicuous central polymorphonuclear leucocytic accumulations and necrosis. Stainable tubercle bacilli were present in almost all reactions, but they were slightly more numerous in the lesions of the adult guinea pigs.

Group 2: The tissue response in animals autopsied at intervals after

birth tended to duplicate the extent and character of the disease seen in the adult control animals. Immediately after birth the reaction simulated that of the foetus, but with increasing postpartum age it approximated that of the adult. Polymorphonuclear leucocytic infiltration or necrosis ultimately appeared in the lesions and the animals finally died from tuberculosis.

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EDITORIAL

The Tuberculous Woman and "Proconception"

We are impressed by the eminently sane and sound position taken by Ernest Mariette in discussing "Contraception in the Tuberculous," a short paper appearing elsewhere in this issue (1). Doctor Mariette was addressing a nonmedical audience, the Minnesota Birth Control League, most of whose members and guests presumably had at least passing familiarity with the contraversial subject of "Contraception" in general. It was neither his duty nor his task to weigh the almost innumerable and perhaps irreconcilable sides of this difficult general subject—difficult, if it is to be discussed adequately. His sole objective lay in putting plainly before his hearers how the medical profession should proceed in the presence of one of the most common situations presented to its practitioners—in advising the woman, with active or arrested tuberculosis, concerning entrance into the married state and the fulfillment of a—if not *the*—prime obligation of marriage. In this Doctor Mariette succeeded admirably in presenting the positive side of contraception. Mindful of the fact that pregnancy need not spell the doom of the tuberculous woman; realizing, on the other hand, that it may only too frequently weight the scales against future or sustained recovery from tuberculosis, he believes it every tuberculous woman's right to be allowed the best available contraceptive advice. He would instruct every patient desiring information; he would not force this on anyone, "If for any reason the woman does not desire it." But, he urges, "The married woman with tuberculosis must have more than an admonition to prevent pregnancy; she must have the best," coming from medical sources, the physicians, and consisting of "definite advice about the scientific methods of avoiding pregnancy," of which, in his opinion, "we give them little."

It is the usual thing for the woman with active or arrested tuberculosis to consult her physician about marriage, especially if this possibility impends: not infrequently her fiancé also enters actively into the discussion. No one with experience need tell the practising physician

the almost universal result of such a conference:—if the parties concerned are set upon marriage, they marry, despite any advice, unfavorable though this be. This consequence is among the surest things that the physician knows. Yet, much though the physician may deplore the rejection of his opinion, he is perfectly safe in case the result turns out unfortunately. The burden of blame cannot be his: this must rest strictly upon those who refused to follow his counsel.

In the matter of contraception, the physician is again always on safe ground if he advises against conception; for a woman who does not conceive cannot possibly have her tuberculosis unfavorably influenced by a pregnancy. Whether or not contraceptive advice, successfully followed, deprives the patient of compensating advantages is another question, and need not be gone into here. But, in the single big business of preventing, or perhaps allaying, active tuberculosis, that physician treads the solidest ground who counsels "no conception:" and this is likely to remain true until we possess a reasonably accurate test on the effect of pregnancy on tuberculosis. Viewing the situation realistically, Doctor Mariette is probably correct in his opinion as to the deficiency of present practice,—that we, as physicians, are accustomed to be too indefinite and perhaps careless in giving advice "about the scientific methods of avoiding pregnancy."

There is a great deal that might be said about what is really quite a large subject, however much we would limit the question. But, when confronted by the problem under discussion, we should, above all, be practical,—in trying to proceed in that way that may avoid dangers which we know exist, yet as to which we cannot predict precisely where they may arise. We have only generalities of prognosis to go on, and it is only through and by generalities that we can advise prophylaxis. From this single point of view, our *routine* duty would seem to be unmistakable. When we advise against marriage, we are aware that almost always our counsel will not be followed: however, we can share no blame in a disastrous result. In the state of present knowledge and practice, we should, as a working rule, probably advise contraception, simply because tuberculosis, aggravated or reactivated, is bound to result in so large a proportion of pregnancies and their accompaniments, as to allow too free and unconsidered a deviation from the rule an insufficient margin of safety. And, in practice and performance, the case could hardly be put better from the medical side than it has been by Doctor Mariette.

But there remains another, and not inconsiderable side of the whole question of the tuberculous woman and conception, and particularly her medical management in the circumstances. This has to do with medical advice that would permit and even counsel conception in the woman with tuberculosis.

For, however large may be the proportion of tuberculous married women who may welcome contraceptive advice,—and this with or without any reference to their tuberculosis,—the proportion of women with tuberculosis who crave parenthood is not inconsiderable, and such women also consult physicians concerning marriage and child-bearing. In these instances, the conscientious therapeutist will try to serve every best interest of his patient: he will surely not be unmindful of other features, more or less tangible, besides those of danger of relapse or aggravation of the tuberculosis, that may enter into the situation: he will consider the possibilities for evil that enforced deprivation of parenthood may erect in some women, not to mention their marital relations. Wives (and husbands) are of every imaginable kind in their responses to sterility, especially if this is not inevitable. There are not a few women who, apart from any inhibitions imposed, say, by religious piety, will undergo gladly any risk in order to mother their own children. As physicians, we must minister to these normal impulses and needs to the utmost possible extent. We face a condition which we must meet; and our problem is how and to what extent we may proceed—and this with a minimum of hazard to our patients.

In meeting the problem there would seem to be no general rule to be applied—no general rule except possibly in the presence of one or two conditions. It is questionable whether the possibility of pregnancy should be countenanced, first, for any woman during a period when she is actively tuberculous; or, second, for any woman, with any history of tuberculosis, during a period when she—her family—is laboring under telling economic stress. Any advice that would permit conception in the tuberculous will, naturally enough, be hedged with "ifs," "buts," and "provideds," but there can be no reasonably safe "ifs" and "buts" for the sick or pauperized tuberculous woman. So much would seem plain.

Accordingly, any remarks that follow are directed to the consideration of procedure for those fitted to meet conditions that must be imposed—that is, for the intelligent, and the temperamentally and economically able. What is there that may best guide and establish our advice to them?

With few exceptions these will be women who have had active tuberculosis or who may be or have been "under suspicion" yet without unquestionable diagnosis. Of these, some may have had pregnancies and children in the past, but by far the largest number will have been without antecedent pregnancy or labor. In advising them, the physician's procedure will vary accordingly; but, in any event, he must "individualize" the case.

In the whole realm of tuberculosis, there is no field more ill-defined and more treacherous than that of prognosis—of foretelling what may happen, especially to a case of clinically arrested tuberculosis under any set of given or imagined conditions. It is true that, the longer a case of tuberculosis continues in arrest, the greater are the probabilities that it will stay arrested,—increasingly so, and under a heavier burden of reactivating factors, as we are accustomed to understand the latter: this is one of our best-appreciated *general* facts. But it is also true that individual cases, only too numerously, relapse, under entirely unexpected conditions and after astonishingly long intervals since the establishment of clinical arrest. However, the general fact remains,—to serve (as it should) as one of our best guides in helping to direct the activities and life of the "arrested" patient.

Which is to say that the best earnest we possess of what a person with tuberculosis *will* do is what she *has* done with her tuberculosis—how she has kept "in balance" with it—in the past. Appreciating this, we begin to understand how supreme will be the part of an accurate and comprehensive knowledge of a patient's past, particularly as this is pertinent to her tuberculosis, in attempting to estimate probabilities that concern as definite an influence as conception and pregnancy can exert on tuberculosis.

In other words, one cannot bring to the task under consideration too much well-sifted and well-appraised a comprehension of the "give and take" between a patient's old tuberculosis and herself. Here is an exercise in which the art of medicine must prevail.

In the case of a tuberculous woman who may have been pregnant before, the same care and assiduity must mark the physician's endeavors to acquire clear and complete information on how she tolerated the pregnancy. A history, for instance, of marked toxaemia would surely set the physician to thinking differently than would a story of unimpaired or even improved general health during the pregnancy: indeed, two such opposite experiences suggest two different soils in which rooted tuberculosis may attempt to flourish again.

If conception is to be countenanced for the tuberculous woman, such advice must always emphasize the proviso that any pregnancy must be managed throughout its term as a special and unusual case, and with the means and facilities at hand for perhaps "over-invaliding" the woman, should this course appear the safer: with, also, the understanding that all possible chances of the complications of parturition are to be avoided or reduced to a minimum.

Ideal conditions would presume a close coöperative management of every pregnant tuberculosis patient's case under the joint care of specially interested and understanding internist and obstetrician,—from the moment of diagnosis of pregnancy to the end of the puerperium. It would even be better if the obstetrician "entered" the case at the time when permission to conceive first came under discussion between patient and physician.

From the point of view of the patient's best interests, such would seem to be minimum requirements. Are they too ideal to be put into practice—too expensive, for instance, for all but an insignificant fraction of patients who seek advice?—Maybe so, under present "loose" conditions: nevertheless, they point to one more field in the realm of tuberculosis practice which organizations for the care of the tuberculous—our sanatoria and dispensaries, for example—might profitably cultivate and exploit, and within no long time bring within the reach of the responsible patient of average means and intelligence.

Here again Doctor Mariette's remarks are suggestive. If (as he relates) trained physicians can be delegated from his public sanatorium (Glen Lake) to act as technical advisers in the matter of contraception, there would seem to be no good reason why essentially similar "machinery" cannot be developed in the management of what we may call "proconception." To succeed reasonably in this task will surely entail a vaster experience, a rarer judgment and greater difficulty in general than to carry the message and technique of contraception to justly fearsome women; yet, even so, we have a sneaking idea that it might prove to be a more welcome duty for the members of "our Staff," than Doctor Mariette's remarks would seem to indicate concerning their attitude toward their present "procedure".

A. K. K.

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FURTHER STUDIES ON PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN[1,2] (P. P. D.)

Its Diagnostic Value and Keeping Qualities in Dilutions

ESMOND R. LONG AND FLORENCE B. SEIBERT[3]

During 1934 and 1935 approximately 150,000 doses of the Purified Protein Derivative of tuberculin were distributed through the auspices of the National Tuberculosis Association and its affiliates, on the basis announced when the product was introduced (1). It has not been possible to secure returns on all of the tests performed with this material, and a considerable percentage of the records duly turned in were faulty through failure to carry out second-strength tests on nonreactors to the first strength. However, about 60,000 record cards have been received, with full data as requested by the National Association, and the statistical staff of the Association is analyzing these at the present time. It is planned five years hence to make a similar extended survey.

In addition, records of about 35,000 tests are available, in which the test was performed with perfect accuracy and the ages of those tested and the percentage of reactors and nonreactors were recorded, but family and other pertinent data requested for the Association's statistical compilation were not obtained. Included in this group are the results of 27,000 tests on students in American colleges, forwarded directly to the Henry Phipps Institute on the basis of coöperative arrangements made by the Institute and members of the College Hygiene Association. Included also in the 35,000 are the results of some 4,000 tests on American Indians made by members of the staff of the Henry Phipps Institute in various parts of the United States.

The records of tests on 7,000 other American Indians are included in the 60,000 cards returned to the National Association. Partly in the collection of 60,000 held by the Association and partly in the assemblage

[1] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

[2] Presented at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, April 24, 1936.

[3] The Henry Phipps Institute, University of Pennsylvania, Philadelphia.

at the Henry Phipps Institute are records of a considerable number of tests from outside continental United States, including about 2,000 from Puerto Rico, 5,000 from American Samoa, 4,000 from Korea and 1,000 from Great Britain and continental Europe. The results of tests with Purified Protein Derivative in 800 Bush Negroes from the upper Aucaner jungle country of Dutch Guiana have been reported by Kahn (2).

DIAGNOSTIC VALUE OF PURIFIED PROTEIN DERIVATIVE IN STANDARD DOSES

The majority of surveys with the Purified Protein Derivative have been supplemented, to some degree, with X-ray studies. The usual procedure is to X-ray the positive reactors only. Occasionally a study is made in which all of the reactors and nonreactors are X-rayed. Further studies of this complete character are desirable. More often the reactors and a certain unselected portion of the nonreactors are X-rayed. We have reported one such study ourselves (1). In general, investigations of this character have yielded few positive X-ray films in the presence of a negative reaction to the Purified Protein Derivative. Occasionally, thoroughly calcified lesions are found in cases in which the reaction to Purified Protein Derivative is quite negative. This is true in the case of any tuberculin. Using a sample of Old Tuberculin of strength which has since been repeatedly checked in comparison with the Purified Protein Derivative, McPhedran and Opie (3), in a study of a thousand families in the clinic of the Henry Phipps Institute, found calcified tuberculous foci in approximately 5 per cent of persons failing to react to tuberculin. In conformity with general opinion they regarded these lesions as obsolete.

It is more important to know if any significant clinical tuberculosis fails to be detected by tuberculin. In the long investigation just cited, McPhedran and Opie recorded that "the absence of reaction to tuberculin excludes with scant error the presence of infiltrating tuberculous lesions and indicates the absence of potentially progressive tuberculosis."

Many studies have recently been made or are in progress on the accuracy of Purified Protein Derivative in detecting clinical tuberculosis. In a number of these an attempt is being made to locate a single dose of Purified Protein Derivative suitable for the detection of clinical tuberculosis without unduly severe reaction in the most sensitive patients. Only two of these studies of the value of different doses in

detecting clinical tuberculosis will be described here, one by ourselves and one by Plunkett and Siegal (4), reported before the Clinical Section of the National Tuberculosis Association in April, 1936.

The study by ourselves covers Purified Protein Derivative tests on 1,867 white and colored patients entering the clinic of the Henry Phipps Institute for the first time in 1934 and 1935. The data were kindly assembled for us by Drs. Gaetan, Vivas, and Sosa, Fellows of the International Health Division of the Rockefeller Institute at the Institute. Not all of the 1,867 were X-rayed, as in many cases there was no indication for it. Seven hundred and twenty-seven positive reactors, in

TABLE 1

Diagnostic value of purified protein derivative in active and latent tuberculosis

	NUMBER OF PATIENTS	POSITIVE TO 0.000,02 MGM.	NEGATIVE TO 0.000,02 MGM. POSITIVE TO 0.005 MGM.	NEGATIVE TO BOTH DOSES
Total cases tested with Purified Protein Derivative	1,705	—	—	—
X-ray positive	498	458	30	10
Minimal	35	34	1	0
Moderately advanced	105	102	3	0
Far advanced	127	122	4	1
Latent apical	104	88	13	3
Suspected apical	30	24	4	2
Active childhood type	14	10	2	2
Calcified childhood type	83	78	3	2
Totals	498	458	30	10
Total in per cent		92	6	2

whom there was some reason to suspect the presence of tuberculosis, were X-rayed. Four hundred and eighty-eight of these were diagnosed as X-ray-positive for tuberculosis. In addition, 30 clinic patients negative to the Purified Protein Derivative, but in whom there was some reason to consider tuberculosis, were X-rayed. Ten of these were diagnosed as having active, latent or suspected tuberculosis of adult type or childhood-type calcified tuberculous lesions. Six cases of nonpulmonary tuberculosis were found, all of which reacted to the first dose of the Purified Protein Derivative. Table 1 records the distribution of the 498 pulmonary cases according to advancement and character of lesion and reaction to the Purified Protein Derivative. Of the

488 positive to both Purified Protein Derivative and X-ray, 458, or 94 per cent, were positive to the first dose (0.000,02 mgm.). In 10 cases in which the X-ray diagnosis was recorded as positive or probably positive for a tuberculous lesion, the reaction to Purified Protein Derivative was negative. One of these was diagnosed as an advanced case, but it was an unusual one, recorded by Dr. McPhedran as atypical by X-ray. Tubercle bacilli were noted as present in the sputum in only two of a large number of examinations, and very scanty in occurrence on these occasions (Gaffky I). The patient subsequently entered a sanatorium, where a diagnosis of moderately advanced pulmonary tuberculosis was made, although the sputum was always negative. The patient was not seen after October, 1934. It remains possible that the X-ray diagnosis was wrong in this case.

In one of the two cases of childhood-type tuberculosis noted, in which the reaction to Purified Protein Derivative was negative at the time the lesions were first seen by X-ray, subsequent reaction to the Purified Protein Derivative was positive. It is interesting to note that likewise, in one of the two cases of childhood-type tuberculosis reacting at first only to the second dose of Purified Protein Derivative, subsequent test was positive with the first dose.

In the three cases diagnosed as latent apical tuberculosis on the basis of scanty salients in the upper third of the lung in the X-ray film, it was not possible to secure later tuberculin tests, as the patients did not return. This is also true of the two cases recorded as suspected adult-type tuberculosis. There is nothing surprising about the insensitiveness or low sensitivity of certain of the cases with calcified lesions of first infection. This is a common experience.

In the summary of this study, it may be said that in this series very few cases of clinical significance were missed by the Purified Protein Derivative, and that the overwhelming majority of those patients diagnosed tuberculous not only reacted to the Purified Protein Derivative, but responded to the minute first dose (0.000,02 mgm.).

The other study to which reference will be made is that reported by Plunkett and Siegal (4). This study, in which only the positive reactors were X-rayed, had the noteworthy superiority of intensive transaction in a brief time, ensuring a uniform technique throughout. In this investigation 1,747 inmates of the Newark State School for the Feeble Minded in New York were tested with Purified Protein Deriva-

tive, and the 1,069 positive reactors were X-rayed. Twenty-six cases of adult type pulmonary tuberculosis were discovered, 24 of which reacted to the first dose of Purified Protein Derivative and 2 to the second. There were 4 cases of first-infection or childhood-type tuberculosis, all of which reacted to the first dose. Seventeen cases were recorded as of suspected tuberculosis, all of which were positive to the first dose. Seventeen cases were reported as having old fibrotic apical lesions, three of which reacted only to the higher dosage. Calcified lesions of childhood-type infection were diagnosed in 76 cases. Ten of these required the higher dosage to elicit positive reaction.

The latter investigation, to which reference will be made again, like our own, and like several series of cases we have published previously (5), shows that the great majority of ambulant patients with pulmonary tuberculosis, known or discovered in the course of routine survey, react to the first of the standard doses of Purified Protein Derivative. This is quite in accord with the results secured by Ayman (6), in comparing the size of reactions to a high dilution of Old Tuberculin in clinically tuberculous and nontuberculous adult patients. That somewhat different results may be secured in tuberculous and nontuberculous children has been shown by Stewart (7).

However, extended study has shown that extremely ill patients and a considerable number of patients with chronic far-advanced tuberculosis of long standing may not react to tuberculin. This holds for the Purified Protein Derivative, as well as tuberculin in other forms. In a study to be reported in detail later on 116 patients with advanced tuberculosis tested at monthly intervals in the Philadelphia General Hospital over an average period of six months, 31, or 27 per cent, were negative to the first dose of the Purified Protein Derivative two-thirds of the time or more. While most of this group occasionally reacted to the first dose of the Purified Protein Derivative, eight of them were negative to the first dose throughout their whole course of several months in the hospital. Almost all patients reacted to the second dose at some period of the course. In those patients dying of tuberculosis in the hospital during the period of study, the reaction to the Purified Protein Derivative was commonly negative for two months before death. These results in general also conform to the results of Ayman, who found that the "poor reactors were almost invariably advanced or moribund cases."

DEGREE OF NONSPECIFICITY IN REACTION TO LARGE DOSES OF TUBERCULIN

Since the small first dose of Purified Protein Derivative elicits response in the majority of patients with clinical tuberculosis, it may be asked by some why so much stress is laid upon injection of all nonreactors to the first dose with a second, much larger dose. The answer is, first, that a few important cases of progressive tuberculosis are discovered, as noted, and, second, that many cases of infection, not clinically important at the moment, but significant as evidence of more or less serious contact, are uncovered. In surveys of children the importance of this infected, but less hypersensitive, group becomes apparent. In fact, in this group the second test often brings to light as many reactors as the first test. That is, if only the first dose were employed, half of those conventionally considered infected, on the basis of the tuberculin reaction, would not be discovered. The evidence of past years has shown that numerous contact cases are in the second half.

It is true, however, that there is a definite element of nonspecificity in the apparent positive reaction to the second dose. While numerous cases of serious contact, demanding separation of the source of infection and the recipient, often are not sufficiently hypersensitive at the moment of the test to respond to the first dose, and therefore require the second for discovery, it seems probable that at the same time the second places on record fully as many which are of no significance as far as tuberculosis is concerned. This nonspecificity is suggested by experiments in which simultaneous tests are made with a purified protein derivative manufactured, not from the tubercle bacillus, but from another acid-fast organism, for instance, the timothy bacillus or a stock strain of leprosy bacillus. The following experiments with the timothy bacillus illustrate this:

An experiment was carried out on the freshmen, 99 in number, in a small college in eastern Pennsylvania. The students tested came for the most part from Philadelphia, its suburbs, and small towns in eastern Pennsylvania and New Jersey, and were between 17 and 21 years of age. Thirty-nine reacted to the first dose of the Purified Protein Derivative of tuberculin. All 99 were negative to the same dose of the analogous protein derivative of the timothy-grass bacillus. The 60 negative to the first dose of the Purified Protein Derivative were then tested with the second dose (0.005 mgm.) and, at the same time, in the opposite arm, with 0.005 mgm. of the timothy-grass-bacillus product.

Twenty-one of the 60 reacted to the second dose of the Purified Protein Derivative, and 18 of these, that is, 86 per cent of them, reacted also to the timothy-grass-bacillus product. The reactions were of almost identical size, averaging 10 x 9 x 1 mm. for the timothy-grass-bacillus preparation and 9 x 8 x 1 mm. for the tubercle-bacillus product. Three subjects were positive to Purified Protein Derivative and negative to the timothy-bacillus product, and four subjects negative to the former and positive to the latter. Thirty-five of the 99 originally tested were negative to both protein products in the maximum dose.

Eighteen of the 60 boys positive to the first or second dose of the Purified Protein Derivative had lesions diagnosed by X-ray as active, latent or suspected tuberculosis of adult type or calcified childhood-type tuberculosis. Thirteen of these were positive to the first dose, and in almost all of these cases the lesion seen by X-ray was a calcified lesion of primary infection. Five boys were negative to the first dose, but positive to the second, and all five were positive also to the same dose of the purified protein derivative of the timothy bacillus (0.005 mgm.). Three of the five were cases of calcified tuberculosis of first infection; one was a case with a suspected residuum of childhood-type infection; and the other was diagnosed as latent apical tuberculosis of adult type and very slight extent. Of the three subjects positive to the Purified Protein Derivative from the tubercle bacillus but negative to the timothy-bacillus product none was X-ray positive. Unfortunately, X-ray examination was limited to the tuberculin-positive students, and the four boys negative to tubercle-bacillus Purified Protein Derivative but positive to the corresponding timothy-bacillus product were not X-rayed.

At another institution, a boy's school near Philadelphia, 186 boys who were positive to the first dose of the Purified Protein Derivative of tuberculin were divided into two groups and retested with timothy-grass-bacillus protein. The protein in this case was T. P. T., not P. P. D. (see Seibert and Munday (8) for the chemical difference), but this probably is not an important distinction, as in our experience skin reactions to these two protein derivatives are identical. The first group of boys were tested with 0.000,1 mgm. timothy-grass-bacillus T. P. T., and 18 per cent reacted positively. The second group were tested with 0.001 mgm. timothy-grass-bacillus T. P. T., and 72 per cent reacted. Had a still larger dose of the timothy-bacillus product been used, for instance, 0.005 mgm., as in the college group just cited, probably a still larger proportion would have reacted. It is apparent that the majority

of subjects positive to the Purified Protein Derivative of tuberculin will react to timothy-grass-bacillus protein if the latter is used in large doses.

This common reactive capacity to the two protein derivatives (tubercle bacillus and timothy-grass bacillus) might be explained on the ground of a common possession of certain reactive chemical groups in the protein molecules, were it not for the fact that the highly sensitive group reacting to the small dose of tubercle-bacillus protein derivative did not react to the same dose of the protein derivative of the timothy bacillus. Specific cross-reactions due to a small amount of substance in the timothy-bacillus product, identical with that in the tubercle-bacillus preparation, would be expected in the highly sensitive group,

TABLE 2

Tests with P. P. D. at high-school and college ages
Increment from second dose

GROUP AND AGE	NUMBER TESTED	POSITIVE TO 0.000,02 MGM. PER CENT OF TOTAL TESTED	POSITIVE TO 0.005 MGM. PER CENT OF TOTAL TESTED	POSITIVE TO 0.000,02 MGM. PER CENT OF TOTAL REACTORS	POSITIVE TO 0.005 MGM. PER CENT OF TOTAL REACTORS
Santa Barbara High Schools: 10–19 years	752	18	12	60	40
Haverford College Freshmen: 17–22 years	278	39	21	65	35
Papago Indians: 10–19 years	266	66	10	87	13

not confined to the less sensitive subjects, as here. That there may be special significance to the timothy-bacillus protein sensitiveness in some parts of the country is shown by the careful tests of Mariette, Fenger and their associates (9), who have found a considerable percentage of reactors to timothy-bacillus protein in subjects not reacting to the same dose of tubercle-bacillus protein.

The element of nonspecificity thus brought to light may be correlated with the interesting mathematical relationship attending the use of the two doses. At the high-school or college age, the second dose ordinarily adds from 10 to 20 per cent to the figure obtained by the first dose, regardless of what the latter is. If 40 per cent of the pupils of a school are positive to the first test, the second test raises the total to about 60 per cent. If 75 per cent are positive to the first test, the second commonly brings the figure to 85–90 per cent. If only 10 per cent react to

the first test, the final figure is usually about 25–30 per cent. Table 2 illustrates this relationship. As it makes clear, the increment from the second dose, in terms of percentage of total reactors, varies a good deal more than the increment in percentage of total tested, and is greatest where the total number of reactors is least. This is an important fact to recall when survey funds are limited and the tuberculin test is used as a screen in selecting cases for X-ray examination.

THE PURIFIED PROTEIN DERIVATIVE IN INTERMEDIATE DOSAGE

The difficulty of making patients return for second examination and the limitations of the examiner's own time have led many physicians to seek a single dosage of tuberculin that will detect all of the clinically significant cases and all of the significant contact cases, and at the same time not cause a high percentage of severe reactions. The element of nonspecificity in the reaction to the high second dose has given impetus to the search for an effective intermediate dose.

During the past year, extensive trial of intermediate dosage of the Purified Protein Derivative of tuberculin has been made. The doses used by various testors have been 0.001 and 0.000,5 mgm., that is, one-fifth and one-tenth, respectively, of the standard second dose. It has been argued that since the low dose of 0.000,02 mgm. detects virtually all of the clinically active tuberculosis, and from 50 to 75 per cent of the nonclinical contact infection, without causing many severe reactions, a somewhat higher dosage, without increasing the number of severe reactions materially, might bring to light all of the clinical cases and the great majority of the nonclinical contact infections as well.

We have ourselves reported one trial on a small scale of the dosage of 0.001 mgm. Purified Protein Derivative in college students, showing that only about 3 per cent of the total number of reactors were missed by this dose. However, the exceptionally sensitive students were screened out by the standard first test dose of 0.000,02 mgm., so that no information on the severity of reaction to an initial dose of intermediate strength was secured.

Numerous trials of initial test with the standard second dose (0.005 mgm.) have been made, and the results communicated to us personally. In communities of low incidence of infection few severe reactions have occurred, but in some series of tests made elsewhere the percentage of "four-plus" reactions has been very high. There is evidence that what is safe for one part of the country is not safe for all parts.

This is brought out by a comparison of three series of tests in Kansas and New York State. Clifton Hall (10) in Kansas used a dose of 0.000,5 mgm. Purified Protein Derivative with apparently satisfactory results as far as the total number of reactors was concerned, and without an appreciable number of severe reactions. In New York State, on the other hand, where the percentage of the population reacting to tuberculin was twice as high, the number of severe reactions was also seriously higher. Two investigations were carried out in New York State, which may be summarized briefly. Deegan (11) and his associates in the itinerant chest clinics of the Division of Tuberculosis of the New York State Department of Health, used a single dose of 0.001 mgm. Purified Protein Derivative, that is, one-fifth of the standard final dose. Of 3,029 persons tested, 49 per cent reacted to this dose. As might be expected, the percentage of reactors among the tuberculosis contacts was much higher than in the noncontacts. The subjects tested were X-rayed at the same time, and the effectiveness of the dosage of Purified Protein Derivative used was shown by the fact that 96 per cent of those positive by X-ray reacted to this dose. Thirty-one out of 32 cases of active pulmonary tuberculosis found by X-ray, and 227 out of 237 detected cases of healed primary or reinfection tuberculosis, reacted. As already noted, an occasional case of active pulmonary tuberculosis, and a certain percentage of cases of healed tuberculosis with calcified lymph nodes, require the full second dose for the production of a positive reaction.

However, in Deegan's cases a fairly high percentage of four-plus reactions occurred. The percentage of severe reactions was much higher in the contact than the noncontact cases, as might be anticipated. Twelve and one-half per cent of all reactions were recorded as four-plus, the figures being respectively 13.4 per cent of the total reactors for the contact group and 9.8 per cent for the noncontacts.

Results of similar import were secured in the large series of cases studied by Plunkett and Siegal (4) of the New York State Department of Health, to which reference was made above. These investigators, in a comparison with Old Tuberculin tested 1,747 persons with 0.000,02 mgm. Purified Protein Derivative. The original intention was to retest all of them with 0.000,5 mgm., but in 476 cases the reaction to 0.000,02 mgm. was severe enough to make retests with 0.000,5 mgm., or twenty-five times as much, inadvisable. Therefore, only 1,271 were retested with 0.000,5 mgm. Those negative to this dose were finally

tested with 0.005 mgm., the regular second dose. A total of 1,069 reactors were discovered. Seventy-three per cent of those reacted to the first dose used, 20 per cent more to the second or intermediate dose, and the final 7 per cent to the standard second dose. Thus, it may be assumed that the intermediate dose would have been effective in detecting 93 per cent of the total reactors. Among the 1,069 reactors, 140 were found who were positive for tuberculosis by X-ray. One hundred and thirty-five of these, or 97 per cent, were detected by either the first or the intermediate dose. The remaining five cases were examples of calcified tuberculosis.

However, it may be assumed that the 476 patients reacting severely to the first dose would have reacted still more severely to the larger intermediate dose. The final conclusion of Plunkett and Siegal was that more study is needed to select an optimum one-test dose of the Purified Protein Derivative, and that this may be less than 0.000,5 mgm.

While present studies have thus been inconclusive, it seems unwise to use as high a dose as 0.000,5 mgm. in random testing in parts of the United States, such as the East, where the incidence of tuberculosis, and the corresponding number of close contacts, is relatively high. Possibly a dose ten times the official first test dose, or 0.000,2 mgm., will be found sufficiently potent to be practical, detecting 90 per cent of the total reactors without unduly high numbers of severe reactions. In the middle West, on the other hand, and the far West exclusive of the zones that have attracted considerable numbers of tuberculous patients, a single dose of 0.000,5 mgm., that is, twenty-five times the official first strength, may prove practical. It should be remembered, however, that these intermediate dosages, while perhaps suitable for practical case-finding programs, will not have the statistical value of tests performed with the regular two-dose method.

THE KEEPING QUALITY OF DILUTIONS OF PURIFIED PROTEIN DERIVATIVE

The keeping qualities of Purified Protein Derivative are similar to those of Old Tuberculin. Gross bacterial contamination of either one, aside from its intrinsic dangers, has a very deleterious effect on dilutions of the tuberculins and may be one of the chief reasons for the decrease in potency on standing. We have repeatedly seen complete loss of strength due to bacterial growth in unpreserved dilutions and even in concentrated solutions. For this reason, the addition of an amount of antiseptic necessary to preserve absolute sterility is cus-

tomary. Phenol in a concentration of 0.5 per cent is commonly used. Because of the common opinion that this amount of phenol is likely to cause occasional nonspecific reactions, 0.25 per cent phenol is used in the diluting fluid accompanying the Purified Protein Derivative tuberculin tablets. However, repeated tests at the Henry Phipps Institute indicate that absolutely no reactions occur upon the injection of diluting fluid containing 0.5 per cent phenol, provided every precaution has been taken to ensure that there has been no contamination of solution or glassware with tuberculin.

TABLE 3

Keeping qualities of P. P. D. in dilute solution
Size of reactions on opposite arms

FIRST DOSE		SECOND DOSE	
Fresh	After 2 days in incubator	Fresh	After 2 days in incubator
11 x 10 x 1 mm. (22 reactions)	11 x 9 x 1 mm. (22 reactions)	44 x 34 x 3 mm. (3 reactions)	46 x 31 x 3 mm. (3 reactions)
Fresh	After 1 week in incubator	Fresh	After 1 week in incubator
11 x 10 x 1 mm. (21 reactions)	11 x 9 x 1 mm. (21 reactions)	16 x 14 x 1 mm. (6 reactions)	6 x 5 x 1 mm. (5 reactions, 1 missed)
Fresh	After 4 months in ice-box	Fresh	After 4 months in ice-box
21 x 19 x 2.3 (61 subjects) (27 reactions)	13 x 12 x 1.7 (61 subjects) (28 reactions)	15 x 13 x 1.4 (34 subjects) (9 reactions)	15 x 13 x 1.4 (34 subjects) (11 reactions)

That 0.25 per cent of phenol in the diluting fluid does not furnish perfect protection against contamination has been shown by means of the plate method in our laboratory. Freshly made tuberculin dilutions, dilutions kept for two days or a week in the incubator, and dilutions kept for four months in the ice-box, all showed a few "air" colonies in some plates. There was not, however, an increase in the number of colonies corresponding to the time of incubation, a fact probably indicating that this amount of phenol is sufficient to prevent multiplication of the bacteria present, although it is not able to cause death of all of them.

It is possible, however, that the presence of these few bacteria may be partly responsible for the progressive loss in potency of the tuberculin

dilutions occurring with time. For example, as can be seen in table 3, tuberculin (Purified Protein Derivative) which had been diluted and kept in the incubator for two days appeared to be just as potent as freshly diluted tuberculin. Diluted tuberculin kept in the incubator for one week also was as effective as freshly diluted material on the first test. However, in the less sensitive patients, that is, those requiring the second dose for positive reaction, it was not as effective as the freshly diluted material. When the tuberculin was kept in the ice-box for four months after dilution the reactions produced were quite unsatisfactory. The reactions with this kept material were in most cases smaller, but in some cases they were larger and even greater in number than with the freshly diluted material. This false outcome may be accounted for by the fact that atypical, nonspecific reactions were produced by this tuberculin which had stood in the ice-box for four months, even in people giving no reaction with the fresh material. When superimposed upon a true tuberculin reaction, the nonspecific reaction made the tuberculin reaction appear greater than it actually was. As a matter of fact, every bottle of tuberculin kept for this length of time contained a certain amount of sediment which was perhaps the cause of the nonspecific reaction. The sediment, however, did not show the presence of dead bacteria in smear preparations or live bacteria by plating or anaerobic culture.

Therefore, since a stay of two days in the incubator resulted in no detectable loss of strength, as determined by this simple test, it seems safe to use Purified Protein Derivative kept for that length of time. It may be assumed that this retention should be in the ice-box. Presumably another day would do no appreciable harm. This would permit clinics using the Purified Protein Derivative daily to make dilutions twice a week instead of six times, as has been recommended. Rigid precautions, of course, should be taken to prevent bacterial contamination in handling.

SUMMARY

About 95,000 completed tests with Purified Protein Derivative were recorded up to April, 1936. These are being analyzed for future publication.

With a small number of exceptions, patients with clinical tuberculosis react to the Purified Protein Derivative, and the great majority of them react to the first, or smaller, of the standard doses (viz., 0.000,02 mgm.).

The exceptions are for the most part patients with acute tuberculosis or seriously ill patients with chronic tuberculosis of long standing.

A small number of subjects with calcified tuberculous lesions of first infection do not react to the Purified Protein Derivative or other forms of tuberculin.

There is some evidence that a portion of the reactions to the second dose of Purified Protein Derivative, in cases in which the reaction to the first dose is negative, are nonspecific. This statement applies equally to other forms of tuberculin. Reactions to the second dose are elicited equally well by large doses of analogous protein derivatives from other acid-fast bacteria. This appears to be a nonspecific effect, because small doses of the latter protein derivatives do not cause reactions in subjects highly sensitive to the Purified Protein Derivative of the tubercle bacillus. Further evidence of nonspecificity, not yet entirely clear, appears in the fact that the increment of reactions gained by the second dose is approximately constant in terms of the total number of subjects tested, regardless of the number reacting to the first dose.

Some advance has been made in selecting an intermediate dose, detecting the significant reactors without a serious proportion of severe reactions. The safe dose varies for different parts of the country, where different degrees of tuberculization of the population prevail, and for different social groups in the same locality. In communities where less than 40 per cent react to the two doses, a dose one-tenth as large as the standard second dose, namely, an intermediate dose of 0.000,5 mgm., appears practical for case-finding purposes and surveys for significant contacts. However, it is obvious that figures obtained from intermediate dosages will not be suitable for statistical comparison of the reaction to tuberculin in different parts of the country.

Dilutions of Purified Protein Derivative, like dilutions of other forms of tuberculin, lose strength on standing. The loss is probably partly due to mild bacterial contamination, occurring in spite of antiseptic preservation. However, for practical purposes it seems safe to keep the standard dilutions of Purified Protein Derivative three days in the ice-box.

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A COMPARATIVE STUDY OF OLD TUBERCULIN AND PURIFIED PROTEIN DERIVATIVE[1]

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The last decade has witnessed an increased interest in the use of tuberculin in mass-testing of large groups of individuals during childhood, adolescence and early adult life, as found in grade-schools, high-schools, colleges and professional schools. Many data relative to the incidence of infection and disease of clinical significance in different age-periods and in certain environments have resulted from these studies.

Although Old Tuberculin has generally been used, certain inherent and technical factors in its preparation, dilution and administration preclude accurate comparative analyses. One of the most important factors in that regard is that preparations of Old Tuberculin from different laboratories are not always of the same strength. With the development of Purified Protein Derivative from tubercle bacilli grown on a synthetic medium, Long and Seibert seem to have solved this very important problem and at the same time produced a substance which is evidently stable. In view of the apparent advantages of P.P.D. over O.T., the Division of Tuberculosis of the New York State Department of Health decided to test the use of P.P.D. as a routine procedure at its statewide consultation chest clinics. Because of the itinerant nature of these clinics, it was not practical to perform more than one test. After consultation with Doctors Long and Seibert, it was decided to use a one-test dose of P.P.D. equivalent to 0.001 mgm. or one-fifth the usual maximum dose of P.P.D. The results of these tests will be published in the near future. One significant observation, however, is mentioned here because it led to this investigation. Over 12 per cent of the reactors to 0.001 mgm. of P.P.D. showed four-plus reactions.

In view of this relatively high percentage of severe reactions, the State Department of Health decided that further studies regarding the

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specificity, potency, constancy and a practical one-test dose of P.P.D. were necessary.

The Newark State School for Feeble Minded was used for this study, in which the State Department of Mental Hygiene, the Superintendent of the institution and his staff offered their fullest coöperation. The average census of this institution is 1,750, divided roughly two-thirds female and one-third male, and representing all age-groups from three to seventy. Mentally, they are grouped in three main classes,—morons, imbeciles and idiots; and the nationalities for the most part are American, Polish and Italian.

One thousand, seven hundred and forty-seven inmates were tested simultaneously with 0.000,02 mgm. of P.P.D. in one arm and 0.004 mgm. of O.T. in the other arm. Subsequently, with the exception of 476 severe reactors, all were retested in a similar manner with P.P.D. and O.T. twenty-five times the strength of the first dose, namely, 0.000,5 mgm. P.P.D. and 0.1 mgm. O.T. All negative reactors to the second test were then tested a third time with 0.005 mgm. of P.P.D. and 1.0 mgm. of O.T. The interval between tests was one week. All tests were read in forty-eight hours and interpreted according to the recently established standards of the National Tuberculosis Association. A single chest X-ray was taken of every reactor.

At the end of the first test, 44.5 per cent of the total tested reacted to P.P.D., and 18.0 per cent to O.T. Although a few previous tests at the Phipps Institute in an attempt to standardize these two substances had seemed to indicate that 0.004 mgm. of O.T. was comparable to 0.000,02 mgm. of P.P.D., the results of this first practical application of the test undoubtedly showed that the P.P.D. was more potent, which fact accounts for the marked discrepancy of the percentage of reactors.

At the end of the second series of tests, 56.9 per cent of the total reacted to P.P.D., and 54.2 per cent to O.T., that is, there were 47 cases which reacted to P.P.D. and not to O.T. There were no cases which reacted to O.T. but not to P.P.D. The readings at the end of the third series of tests, with the maximum doses of P.P.D. and O.T. used, revealed again that P.P.D. produced more reactors than O.T. The cumulative results of all three tests showed, with P.P.D., 61.2 per cent reactors, and with O.T., 60.4 per cent reactors. (Table 1 and Chart 1.)

A clear concept of the comparative results of P.P.D. and O.T. may be gained from the following: If the total number of reactors, 1,069, is taken as the unit, then the first dose of P.P.D. discovered 72.7 per cent

reactors as compared to 29.5 per cent with the first dose of O.T.; the second dose of P.P.D. produced 93.0 per cent of reactors as compared to 88.6 per cent with the second dose of O.T.; and while the third dose of P.P.D. gave all the reactors, the third dose of O.T. produced only 98.7 per cent. (Chart 2.)

Throughout the entire study, there was evident an apparent discrepancy in the quantitative and qualitative results in the higher dilu-

TABLE 1

Quantitative analysis of reactors by age, sex and dose

AGE-GROUP	TOTAL TESTED	SEX	TOTAL NEGATIVE		TOTAL REACTORS		FIRST TEST—PER CENT REACTORS		SECOND TEST—PER CENT REACTORS ACCRUED		THIRD TEST—PER CENT REACTORS ACCRUED	
			Number	Per cent	Number	Per cent	P.P.D.	O.T.	P.P.D.	O.T.	P.P.D.	O.T.
0–14	478	M 272	210	77.2	62	22.8	12.9	3.7	16.2	15.8	22.8	22.1
		F 206	153	74.3	53	25.7	20.0	9.7	23.3	22.8	25.7	25.2
15–24	629	M 229	99	43.2	130	56.8	37.6	16.2	49.3	49.8	56.8	55.9
		F 400	144	36.0	256	64.0	48.3	18.0	59.5	54.8	64.0	63.3
25–34	256	M 51	12	20.4	39	76.5	62.7	27.5	74.5	72.5	76.5	76.5
		F 205	29	14.1	176	85.9	67.3	30.2	84.4	81.0	85.9	85.9
35–44	233	M 40	3	7.5	37	92.5	60.0	17.5	87.5	82.5	92.5	92.5
		F 193	18	9.3	175	90.7	69.0	28.5	87.6	83.4	90.7	90.2
45+	151	M 35	6	17.1	29	82.9	45.7	17.1	77.1	65.7	82.9	82.9
		F 116	4	3.4	112	96.6	68.1	27.6	94.0	89.7	96.6	92.2
Total	1,747	M 625	330	52.8	297	47.5	30.9	11.8	41.1	40.0	47.5	46.9
		F 1,122	348	31.0	772	68.8	52.0	21.5	65.7	57.7	68.8	67.9
Grand total.....		1,747	678	38.8	1,069	61.2	44.5	18.0	56.9	54.2	61.2	60.4

tions, and a tendency toward comparability in the higher concentrations. Thus, in the first series of tests, there were two and one-half times as many reactors with P.P.D. as with O.T., and at the same time the percentage of three- and four-plus reactors with P.P.D. was two and one-half times as great as the percentage of three- and four-plus reactors with O.T.,—59 per cent to 24 per cent. In the second series of tests the ratio of P.P.D. reactors to O.T. reactors was 1.05:1, and the ratio of percentage of three- and four-plus reactors with P.P.D. as compared

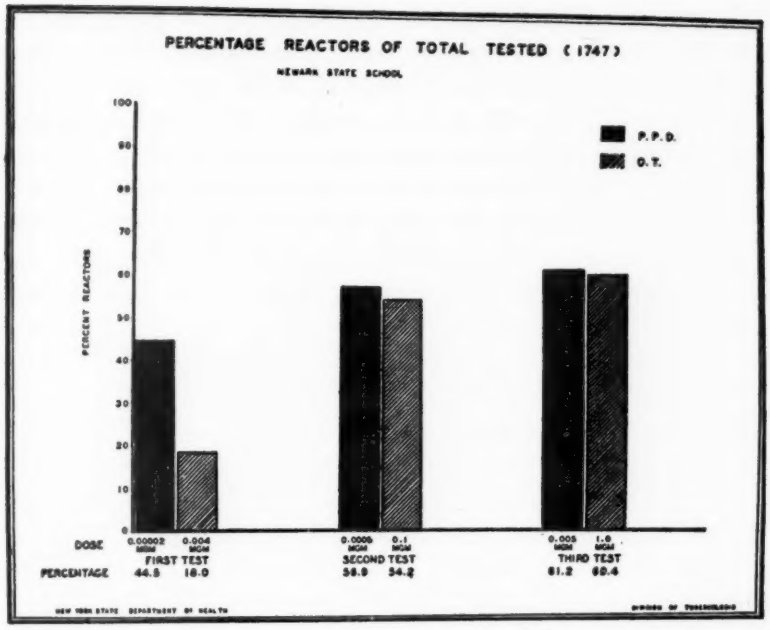

CHART 1

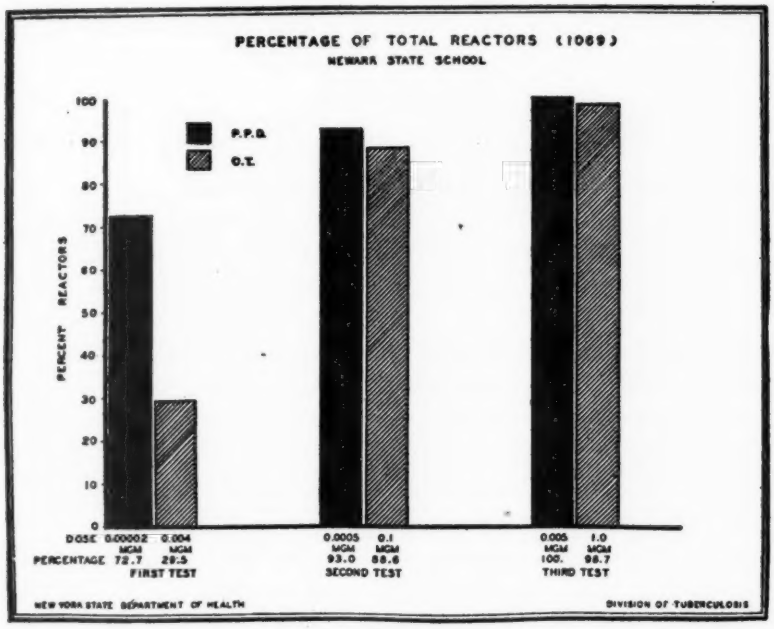

CHART 2

to O.T. was 1.24:1, or 71.5 per cent to 58 per cent. In the third series of tests the ratio of P.P.D. reactors to O.T. reactors was 1.01:1, whereas, the corresponding ratio of percentage of three- and four-plus reactors was 1.38:1, or 19.7 per cent to 14.3 per cent. The increment of reactors with the third dose, however, was comparatively small. (Table 2.)

For practical reasons, most of the three-plus and all of the four-plus reactors at the end of the first series of tests were not retested with the next higher concentrations of P.P.D. and O.T. The first series of tests showed 15 four-plus reactions with P.P.D. or 1.9 per cent of the reac-

TABLE 2

Comparison of purified protein derivative and old tuberculin
Percentage of total group reacting
Percentage of three and four plus reactors
Newark State School

	PERCENTAGE REACTORS OF TOTAL TESTED	PERCENTAGE OF REACTORS WITH 3- AND 4-PLUS REACTIONS
First test:		
P.P.D.	44.48	59.07
O.T.	18.03	24.13
Ratio P.P.D. to O.T.	2.47 to 1	2.45 to 1
Second test:		
P.P.D.	56.90	71.57
O.T.	54.21	57.92
Ratio P.P.D. to O.T.	1.05 to 1	1.24 to 1
Third test:		
P.P.D.	61.19	19.72
O.T.	60.39	14.29
Ratio P.P.D. to O.T.	1.01 to 1	1.38 to 1

tors, and none with O.T. Those who gave three- or four-plus reactions with P.P.D. but did not react or reacted only one- or two-plus to the first O.T. test were tested with the second dose of O.T. but not with the second dose of P.P.D. For this reason, there were fewer individuals tested with the second dose of P.P.D. than with the second dose of O.T.

The second series of tests showed twelve, or 2.3 per cent, of the reactors to P.P.D. with four-plus reactions and thirteen, or 1.85 per cent, of the reactors to O.T. All the four-plus reactors to the second O.T. test, with the exception of one, were in those who did not receive the

second dose of P.P.D. That one exception reacted three-plus to the first P.P.D., two-plus to the first O.T., and four-plus to both second doses of P.P.D. and O.T. It may be assumed, therefore, that the remaining 12 four-plus reactors to the second dose of O.T. would also have given four-plus reactions to the second dose of P.P.D. In addition, a considerable percentage of the three-plus reactors to the first P.P.D. might also have given four-plus reactions to the second dose of P.P.D. What the percentage of four-plus reactors might have been, had the second dose of P.P.D. been given to all those who received the first tests, irrespective of the severity of the reactions, is difficult to estimate. It would have been a considerable proportion,—certainly more than the forty here presented.

Although this study was undertaken primarily for the purpose of evaluating more accurately the practicability of P.P.D. for general use, it was at the same time a complete tuberculosis survey of the inmates of the institution, and the results from that aspect are important.

It was originally intended to test and X-ray all employees. For various reasons this could not be done. Ninety-three, however, were X-rayed. One woman attendant, age 50, showed an old, healed, apical lesion, and another attendant was being treated by artificial pneumothorax. These cases are not included in this report. It is hoped that in the follow-up of this study all the employees will be studied.

Of the 1,069 reactors, abnormal findings with reference to tuberculosis were demonstrated by X-ray in 140 individuals, as follows:

1: Adult-type pulmonary tuberculosis: 26, of which 14 were minimal, 6 moderately advanced and 6 advanced. Twenty-four of these reacted to both first tests of P.P.D. and O.T. One minimal case failed to react to the first tests but reacted to both second tests, and one advanced case reacted only to the second dose of P.P.D.

2: Two cases of first-infection tuberculosis, pneumonic type: Both of these cases were children, ages 3 and 6, and both reacted to the first tests of P.P.D. and O.T.

3: Two cases of first-infection tuberculosis: With evidence of apparent healing or resolution of parenchymal lesions but with the hilar lymph nodes still enlarged. Both reacted to the first tests.

4: Suspicious for pulmonary tuberculosis: 17. Considering the fact that the total number of individuals showing X-ray lesions was 140, the number classified as suspicious is high. Practically all these 17 individuals, however, were either imbeciles or idiots, and the technical difficulties of obtaining inter-

pretable X-ray films of these were great. These films showed movement and all of them showed suggestive shadows which could not be accurately defined. All reacted to the first tests.

5: Old, apparently well-retracted fibrotic or fibrocalcareous apical lesions: 17. None of these was less than 25 years of age. Three of these failed to react to the first tests, two of these three reacted to both second tests and one to the second P.P.D. only.

6: First-infection tuberculosis, healed: 76. These all showed evidence of discrete nodular calcified deposits in the hilum, pulmonary parenchyma or both. Twelve of these did not react to the first tests; five of these twelve reacted to both second tests; five to the second P.P.D. only; one to both third doses only; and one to the third P.P.D. alone.

There were, therefore, at least 28 cases, or 1.6 per cent, which were of immediate clinical significance, requiring medical care or supervision. An additional 19 are under observation for further study, in order to evaluate their clinical status more accurately; the remaining 93 showed old healed primary or postprimary-type tuberculous infections which at the time of the study apparently were of no clinical importance. Of the 140 that showed X-ray lesions, all but two reacted to the first or second tests, and the two that reacted to the third test only showed calcified primary lesions which were clinically unimportant. Eight of these 140 reacted to P.P.D. and not to O.T.; six of these eight showed calcified primary lesions; one showed an old healed adult-type pulmonary tuberculosis; and one showed advanced pulmonary tuberculosis with cavitation in a patient who was acutely ill.

The results of this study seem to point to the following general conclusions: P.P.D. in higher dilutions is apparently more potent than higher dilutions of O.T.; in higher concentrations P.P.D. is comparable to higher concentrations of O.T. Still further study is indicated in order to determine the size of a practical one-test dose of P.P.D. which will produce the maximum number of reactors with a minimum of severe reactions. From this investigation, it appears that such a one-test dose may be less than the second dose of P.P.D., 0.000,5 mgm., which we used.

The authors are indebted to, and gratefully acknowledge the valuable assistance of, Dr. Charles L. Vaux, Superintendent, and Dr. Rose R. Donk of the Newark State School, in the conduct of this study.

THE TREATMENT OF THE CHILD WITH THE ADULT TYPE OF ACTIVE PULMONARY TUBERCULOSIS

A Plea for Compression Therapy[1,2]

MAX GROSS AND S. B. ENGLISH

Throughout the civilized world a marked reduction in the death-rate of tuberculosis of the respiratory system has been noticed. This remarkable change has been evident, particularly, for the past quarter of a century. The factors (1) assigned for this decline have been many, such as intensive public-health education, better standards of living, better resistance of the populace to the ravages of the disease, general decline of all death-rates, etc.

While all of these factors have doubtless greatly contributed towards this decline, very little stress has been placed upon the importance of the earlier recognition of the disease by the use of the tuberculin test and X-ray. Of still greater importance are the isolation and removal of open cases of pulmonary tuberculosis from the homes and the modern surgical approach rendering them tubercle-bacillus-free. This method of isolation of positive sputum cases removes the source of infection from the immediate family and friends, thus reducing the incidence of infection by the tubercle bacillus and a later development of the adult type of disease. Therefore, even though the first infection has already occurred in some members of a family, the removal of an open, contact case minimizes the subsequent development of the adult form.

Our sanatoria have played a very important rôle in the decline of the mortality rate as well as the reduction in the incidence of tuberculous infection. The removal of open cases to a hospital or sanatorium is only one phase of this vital problem. From an epidemiological aspect, the sanatorium has rendered inestimable value. It is the duty of such institutions to use surgical means, such as artificial pneumothorax, phrenicectomy, pneumolysis or thoracoplasty to render patients tubercle-

[1] From the Children's Division of the New Jersey Sanatorium for Tuberculous Diseases, Glen Gardner, New Jersey.

[2] Read at the Clinical Session on Chronic Pulmonary Diseases of the Tuberculosis Sanatorium Conference of Metropolitan New York, Cornell University Medical College Amphitheatre, New York City, April 8, 1936.

bacillus-free. Little is accomplished if the sanatoria merely keep these people and then return them to their previous environment still expectorating tubercle bacilli. Such people are just as dangerous now as they were before. If we can send back every positive-sputum case in a permanently negative stage, then our duty as sanatorium physicians has been fruitful. We can only hope to eradicate tuberculosis in proportion as the patients are sent home with no bacilli in their sputum. Prior to the institution of active therapeutic measures, no more than 10 per cent of our own patients were discharged with negative sputum, whereas now, with proper surgical collapse, from 65 to 75 per cent go home with negative sputum. This is not only true in our own sanatorium, but probably similarly comparable results are seen in other sanatoria. The effect of such treatment with our modern methods is obvious.

All of these factors mentioned have not only lessened the mortality rate, but also the incidence of infection. At the beginning of this century, the incidence of infection among children, as reported by Pirquet (2) and Hamburger (3), was 5 per cent in infancy, and reached 90 per cent when the child attained maturity. The prevalent belief was that, when children reached adolescence, 95 per cent of them were infected. Recent investigations have shown the incidence to vary from 10 per cent in the rural communities to 90 per cent (4) in the larger cities. That the latter is still high has been shown by other investigations. Rathbun (5) has found only 41 per cent of positive reactors to the tuberculin test. Chadwick and his coworkers (6) have found that 28 per cent reacted to the tuberculin test. Our examinations have shown that about 18 per cent reacted in the smaller communities to an average of 38 per cent in the larger communities and colleges (7). The former consisted of grammar-school children, while the latter group consisted of high-school and college students. It has been further shown that the incidence varies in the same cities, depending upon the class of children tested, the poorer class presenting an increased percentage of reactors (8).

During these investigations, it has been shown that the adult destructive disease is present either in the latent form or active form in anywhere from 0.5 to 3.4 per cent of children having this type (9). The literature is too voluminous to mention extensively; nevertheless, one is impressed with the number of cases having parenchymal, destructive disease in the routine tuberculin-testing of children. The amount of disease present in silent form is surprising. Due to the lack of signs or symptoms, children

are not made aware of their disease. Unfortunately, when such signs or symptoms appear, the disease is in a practically hopeless condition for therapeutic approach.

We frequently read that the death-rate in pulmonary tuberculosis has been markedly reduced, and we become very optimistic. This impression is soon marred by another statement that the death-rate in juvenile patients is still high and does not follow the general decline seen in adults (10). Why should the death rate in the 'teen ages assume such a high peak? We are told that this sorry situation is due to poverty, lack of proper food, poor physical development, exposure to colds, etc. (11). It has been further shown that the death-rate among juvenile females is much higher than among the males of corresponding ages (11). The reasons given, in addition to the above mentioned factors, are various fads in diet, endocrine imbalance in the adolescent period, and the increasing industrialization of women (12). All of these mentioned causes contribute a great deal, but the problem does not seem to be solved.

Why should the adult stand a better chance of survival than the juvenile subject? Yet, such a state of affairs is seen in all institutions handling adults as well as children. Intimate contact, dosage, recent allergy, the spacing of infections and reinfections may explain some of this. Perhaps, some biological reaction takes place in these children which we are unable to explain at present. We are impressed with the observation that the child often seems to harbor the destructive disease in the chest, and yet has a better sense of well-being than the adult, although the disease is apparently the same in both. The disease seems to be more silent in these children in spite of the fact that evidence of activity exists. The symptoms in a large percentage of the cases seem to be more lacking than the signs. When the disease in juveniles becomes manifest, with signs and symptoms, the condition is so far advanced that it presents a hopeless problem. Why, then, should we wait until the disease becomes manifest? If the disease shows some progression, would it not be better to use the modern methods of collapse therapy immediately? We believe that the sooner such methods are used the better the chance for the survival of the patient and that the frightful mortality rate would be lowered.

A common observation expressed by most phthisiologists is that, once the adult destructive type of disease starts, it progresses to a fatal termination unless some active form of therapeutic collapse is instituted. One great drawback to an early application of such therapeutic measures

is the insidiousness of the disease in a large number of such juvenile patients. Practically all minimal cases observed by us have been silent, and have been discovered accidentally by means of a routine tuberculin test and X-ray. Such observations can be substantiated by all those doing this type of work. A good proportion of moderately advanced cases have been discovered as having no signs or symptoms. Neither the family nor the child was aware of the disease.

How can we remedy such conditions? The detection of early cases of adult tuberculosis is of paramount importance. Every moderately to far-advanced case must have been a minimal case at some time during the reinfecting stage. If really early cases were discovered, the use of therapeutic collapse could be dispensed with in the majority of cases. Such people would merely require a period of bed-rest in order to get the lesion under control. No doubt, even some such strictly bed-rest cases will progress and finally require collapse therapy. Since we are unable to pick out most early cases by mere physical examination, other means at our disposal must be used. The tuberculin test and the X-ray can easily help us solve this problem if conscientiously applied in routine mass examinations. Especially do these measures become important in contact cases.

The tuberculin test, plus the X-ray, will at first reveal our primary cases of childhood infection. Such children do not necessarily require hospitalization unless a pneumonic process or a pleurisy with effusion exists. Stewart (13) has expressed the opinion that children harboring a childhood infection need no special care irrespective of whether the case is early or latent. Myers (14) holds the same viewpoint. While we agree with them in most of their contentions, we nevertheless feel that children, possessing a great degree of allergy or having an active primary infection, should be taken care of in some sanatorium for children. We realized many years ago that it made no difference whether children were sent to a preventorium or stayed at home. Discrimination should be used to the extent that only cases with marked allergy, poor home environment, definite contact cases where the open case refused to go to a sanatorium, should be accepted.

Inactive cases of childhood infection should be closely watched from time to time. As soon as the first sign of the adult form appears, they should be immediately hospitalized in an institution equipped to take care of them. If we are to accept the figures of Rathbun (15), that 3 or 4 per cent of such cases furnish us about 75 per cent of our adult cases

later in life, then such measures of frequent reëxamination with the roentgenogram is very vital. Myers and his coworkers (16) have shown that 10 per cent of the childhood-infection cases, within a period of ten to twelve years, develop the adult disease. They believe that approximately 20 per cent of the tuberculin-positive children will develop the adult form during adult life. Hill (17) has shown that 20 per cent of his infection cases developed the adult form. Hence, a first infection becomes a serious condition. It may be considered harmless were we able to prevent reinfection. This, however, is impossible of fulfilment.

After having discovered the adult form in these children, they should be sent to a sanatorium or hospital, equipped to take care of them. In the minimal cases, strict bed-rest plus hygienic-dietetic treatment will suffice in the majority. In those showing progression of the lesions, therapeutic collapse should be instituted immediately. The moderately advanced cases and the far-advanced cases should receive, as soon as possible, some form of active surgical collapse. It has been repeatedly shown that mere routine sanatorium care is inadequate in children harboring the destructive disease. Most of the moderately and far-advanced cases give a very unfavorable prognosis. Bed-rest, plus sanatorium care, does not seem to arrest the disease in a large majority of these cases. Why then temporize with such patients?

Opitz (18) has shown that the prognosis in open cases is grave. Of his series of cases over 10 years of age, 7 per cent are alive, whereas from 25 per cent to 50 per cent of those receiving in addition some form of collapse therapy are alive. Morgan (19) has shown the uniformly poor results on routine care. However, his compression cases are disappointing because the cases treated were so far advanced that nothing could stop the progression of the disease processes. Similarly poor results have been shown on routine sanatorium care by Karan (20). Brock and Mullen (21) have demonstrated the unfavorable results in the noncompression cases and the encouraging results from collapse therapy. Nalbant (22), in a survey, has shown that, when rest treatment alone was used, the mortality rate was around 87 per cent, while in the compression cases the mortality was reduced to 42 per cent. In a series of 215 of our cases, between the ages of 5 and 15 years, having positive sputum, treated only by rest, 73 per cent are known to be dead within a period of ten years. Similar reports are given in favor of compression therapy by such European authorities as Armand-Delille and his coworkers (23), Wolf (24), Perera y Prats (25), Zadek and Son-

nenfeld (26), Cassetta (27), Walle (28), Hartmann (29), Stobie (30) and Pentagua (31).

All of the above authors stress the value of artificial pneumothorax, phrenicophraxis, pneumolysis and thoracoplasty in the treatment of the adult disease in children. These procedures are harmless. Collapse therapy has been found to be the surest means at our disposal of preventing the spread of the disease. Of great value is the early diagnosis, thus allowing intervention before the lesions become diffuse and extrapulmonary complications set in. Desperate cases at times show unexpected improvement from clinical, bacteriological and roentgenographic standpoints. If careful attention is given to the technique, such accidents as air embolism, cardiac disturbances, pleural shock or spontaneous pneumothorax can be reduced to minimal proportions.

In this country, we have been extremely slow in adopting these surgical methods for the treatment of the adult, destructive form in juvenile patients. These methods have proved fairly successful in other countries. Attempts have been made to treat such unfortunate children in most of our sanatoria with rather an air of scepticism and disappointment. The trouble is that the collapse is applied late. We do not give it early enough to expect any good therapeutic effect. Furthermore, many cases when first seen are too far advanced. When we do get an early case, amenable for compression, we temporize and give the usual sanatorium care. The result is that some will progress and become hopeless. There is always that desire to allow nature to take its course. However, there are many children, in fact most of them, who cannot be kept as strictly bed patients in the sense that adults can. Many of them do not feel sick enough and hence will not adhere to a strict bed-rest regimen. No one can deny that a certain percentage of these children may go on to an apparent arrest without the use of therapeutic collapse. On the other hand, a great percentage will progress in spite of the strict routine. Unfortunately, who can prophesy or pick out the cases that will get better without collapse therapy, or that will progress? If we wait too long, adhesions form which interfere with a successful collapse. If the adult disease is the same in children as in adults, why not institute the same type of therapeutic collapse?

We must not wait for positive sputum to make its appearance before collapse therapy is instituted. If there is a definite pulmonary infiltrate or pathological involvement of a tuberculous nature, procrastination is dangerous.

Profiting by our own sad experience in those cases not treated by compression therapy, we have instituted active and immediate therapeutic compression in all children showing the adult, destructive disease. Of course, this does not apply to the minimal cases unless they show progression. Needless to say, a strict bed-rest regimen is followed, along with the other methods of surgical collapse. This form of active therapy has been used in our sanatorium for the past five years. As we observe the cases treated in such a manner, the problem becomes more hopeful.

Because of the poor results obtained by mere routine sanatorium care, very few juvenile patients were admitted. As time went on, even those who despaired became more lenient and these unfortunate children were admitted to the institution with a little less reluctance. There is still plenty of persuasion necessary to convince the sceptical that these children should have a place in an institution equipped to take care of them. We made an effort in the early part of our work of treating hopeless cases, and the good results were somewhat overshadowed and marred. However, this same reasoning can be applied to the adults. Yet, some of these hopeless cases showed unexpected improvement, and in others life was definitely prolonged.

The results of active treatment of the adult, destructive form in children, as reported by the above-mentioned authors, are uniformly good. Of course, the results are variable, depending upon the type of cases treated. If early cases are treated by collapse measures, the end-results will naturally be excellent. On the other hand, the final results will depend upon whether the cases are moderately or far advanced. In such cases, the good results will be in proportion to the type of cases treated. The evaluation of such active therapy can only be determined in the future. More cases should be treated and reported, so that some estimation of this problem can be made.

We have been treating the adult, destructive disease since 1931 by some form of compression therapy. Two years ago we (32) reported a series of 27 cases treated for a period of three years with four deaths. We expressed our optimism and were inclined very favorably toward such methods of treatment. We have not changed our optimism or enthusiasm since that time. As a matter of fact, for the past five years, we have become more and more hopeful that collapse therapy is the only treatment essential to reduce the frightful mortality in children.

We now can report on a series of 49 cases treated by some form of compression therapy for a period of six months to five years. Their

ages have been from 5½ to 15 years. Patients under five are not admitted to our institution and those 15 years of age or over are sent to the adult division.

This series comprises 28 females, of whom four were colored, and 21 males, of whom nine were colored. There were 2 minimal cases that showed definite signs of progression and should be really included in the moderately advanced group. There were 15 moderately advanced cases and 32 far-advanced cases.

It has been our experience that whenever artificial pneumothorax could be given, the results were far superior to any other type of compression therapy. Twenty-four cases received unilateral collapse with two deaths. Both fatalities occurred in the first month, being far-advanced, hopeless cases. Twelve cases (33) received unilateral compression which required an additional phrenic crushing to help close the cavernous processes because of interfering adhesions. In this latter group, we had 4 deaths, 3 of whom died after two years of unsuccessful collapse of the disease process and one died one year after collapse was started. The last fatality had, in addition, an intrapleural pneumolysis followed by a putrid empyema.

Five cases received bilateral artificial pneumothorax with two fatalities, one case in the above-mentioned group having in addition a phrenic crushing. The other death was a hopeless, far-advanced, bilateral case, and no hope was anticipated even before collapse was instituted.

Phrenic crushing was attempted in cases in which no free pleural space could be found; in cases in which adhesions hindered the successful collapse of the lung; and also in those in which the cavernous process was surrounded by fairly good lung tissue. In 4 of our cases, no free pleural space could be found and, therefore, phrenicophraxis was performed. In 2 cases, the cavities are practically closed and in 2 others no improvement was noticeable. One of these cases has been in another institution in a more or less hopeless condition for the past 20 months and it is a wonder that he is still alive with his extensive amount of disease.

In 4 other cases, phrenic crushing was performed because it was deemed inadvisable to give artificial pneumothorax, due to the far-advanced, hopeless condition of the patients. Two are dead, one having died 6 months following entrance and the other 18 months after admission in another institution. The third case is in poor physical condition, being at home for the past 3½ years. The fourth case has been in another institution for the past 3 years, ambulant but an active case.

Phrenic crushing as the procedure of choice was done in one case. The cavity closed and, on investigation, we find that this patient has been in a C. C. C. camp, having been discharged from the sanatorium about 3 years ago. He is in excellent shape.

Of the series of 49 cases, 9 are dead, a death-rate of 18.3 per cent. All of the fatal cases had persistent, positive sputum, marked pulmonary involvement, and cavernous processes, making it impossible to get the disease under control from the very start. They were all progressive cases.

Of vast importance, from an epidemiological aspect, is the fact that we had 34 positive-sputum cases, or 69.4 per cent of the entire series. All of the fatalities occurred in those having persistent positive sputum. Eight cases with positive sputum are still alive. Four of these cases are under treatment a little less than six months, and in two of them there is a tendency for the number of bacilli to decrease. They will become negative cases as soon as the disease process is successfully collapsed. Seventeen, or 50 per cent, became free from their bacilli, and have remained so for over a period of 2 to 3 years. If we deduct the 9 positive-sputum, fatal cases, we have left 25 cases, of whom 17 are bacilli-free (68 per cent turned negative and 32 per cent are still positive). It is noteworthy to mention that many of these children were discovered while going to school. One can only surmise the damage done by these children to others while having positive sputum during their intimate associations with their fellow students.

We have entertained a notion for many years not to mix the cases expectorating tubercle bacilli with those that never had positive sputum. As noted in our entire series, 30.6 per cent never had tubercle bacilli and yet among them were some far-advanced cases. Yet, we never attempted to treat the two together in the same ward. As soon as a previously positive patient becomes negative, he is placed in a different ward with others also having negative sputum. We believe that cross-infection from one to another can occur if positive and negative cases are indiscriminately put together. A contralateral spread should not always be blamed on the diseased side, especially if the so-called diseased lung has been under good compression and the patient remains negative for a definite length of time. We know of 2 cases, being compressed for over 18 months and remaining negative, that developed a contralateral lesion with positive sputum. Those children were exposed to positive cases elsewhere, and we believe that reinfection occurred on the contra-

lateral side because of cross-infection. While it is hard to prove such an assumption, such possibilities and dangers must be considered. This should not only hold true for children, but also for adults who are mixed. Segregation may be a difficult task, but it should be done whenever possible.

Another important fact is that 39 cases in our series had cavities ranging from ½ to 3½ inches in diameter. Eleven of these had multiple cavitation. In five, both lungs exhibited cavities, and in six there were multiple cavities in the same lung. We were successful in closing the cavities in 21 cases, or 54 per cent. The cavities are still open in 9 cases, three of which are in other sanatoria. (Of the 30 living patients with cavities, 21 are closed as mentioned, a percentage of 70 per cent.)

At present, 15 cases are in our institution and 5 others are in different county sanatoria. Of our own cases here, 12 are in very good condition. The remaining three so far show a poor prognosis. Of the 5 cases that are confined in different sanatoria, two are in very good condition, while the remaining three are just about holding their own and must be considered as more or less hopeless cases. That leaves 20 cases that are at home. As far as our recent inquiry goes regarding these juvenile patients who have been discharged for a period averaging from 6 months to 3½ years, we have been able to trace every one of them. Of this group, only one case (a phrenic crushing alone) is in a hopeless condition. Some still continue to take pneumothorax. One of the latter, a female now 18 years old, has been married for about a year and is able to carry on her work as any other normal girl.

Twenty-four of our cases had bilateral disease on entrance. As mentioned before, 5 cases received bilateral artificial compression. The remaining 19 cases had a predominant lesion on one side and collapse therapy on the most involved side seemed to take care of the contralateral lesion.

During the past 5 years, we encountered no accidents and no fatalities were directly due to the technique. No serious complications, such as spontaneous pneumothorax, air embolism, or cardiac embarrassment, have occurred. Three fatalities were due to spontaneous pneumothorax, but in two of them the contralateral, untreated, diseased lung ruptured, and in the third case a spontaneous pneumothorax followed a pneumolysis with putrid empyema. No general anaesthetic or hypnotic was required prior to the treatments.

These patients are the most coöperative ever encountered by us in any

group of tuberculous patients. The treatments have had no effect on the physical or mental development of these patients. The physiological processes and development have gone on just the same. The patients have gained in weight and height, and puberty has set in just as in normally growing children.

It is, indeed, gratifying to see the fever, cough and toxaemia disappear as rapidly as the tuberculous process is compressed. Every patient has consistently gained in weight. The weight gain has been from 15 to 54 lbs. There is usually little or no gain at the beginning of the treatments. However, as soon as the toxaemia, fever, cough and rapid pulse disappear, the gain is steady. The usual percentage of patients develop fluid as is routinely observed in adult patients receiving the same type of therapy. In no instance did we have to remove any fluid and, in most instances, a minimal to a moderate amount of fluid was observed. Incidentally, in four cases, the lungs have expanded with absolute disappearance of the original tuberculous lesions.

Due to economic reasons, we cannot print extensive tables to illustrate the various points mentioned in our discussion of the cases treated. We merely wish to call attention to the fact that therapeutic compression should be used more extensively in children having the adult-type destructive disease. We will, however, briefly discuss a number of case histories taken at random from our series.

Cases

I: J. A., a white boy, 15 years old, admitted in October, 1931, with a history of having an attack of "acute bronchitis" lasting for about 3 months. No history of contact with tuberculosis. The only symptom presented was a slight cough since July, 1931. X-ray (figure 1, case 1) on entrance showed a caseopneumonic lesion, at right upper lobe, with a cavity measuring $1\frac{1}{4}$ inches by 1 inch with some contralateral involvement. Artificial pneumothorax was induced November 9, 1931. Compression was satisfactory, but the cavity was suspended by an apical adhesion and could not close. A phrenic crushing was done October 15, 1932, and two days later (figure 2, case I) X-ray showed a rise of the diaphragm and the cavity smaller than on the previous film. Two months later (figure 3, case I) there was a good collapse with closure of the cavity. Two years later, the lung was allowed to reëxpand, and figure 4, case I, shows this very clearly, with total disappearance of the cavity. The patient was discharged in April, 1933, with a gain of 19 lbs. At no time did he have tubercle bacilli in his sputum. As far as we know, he has been in excellent health since discharge.

II: E. McG., a white girl, 9 years, admitted on September, 1932, complaining of weakness, some cough and occasional night-sweats. She lost some weight, and at times had pain in the left side of her chest. No history of contact. X-ray on admission (figure 1, case II) showed considerable mottling in the right upper lobe with a Ghon tubercle under the 7th rib. On the left, we see extensive involvement of upper lobe with cavity 1½ inch by 1 inch. Sputum Gaffky VIII. Ran fever between 99° and 101°F. Pneumothorax was induced within a week. Fever, pulse and toxaemia came within normal limits in about two months. A roentgenogram on November 4, 1932, showed about 50 per cent collapse and the cavity much smaller. The patient had, however, a movable mediastinum, and gomenol was injected to fix it: this was successful. It took almost a year to successfully collapse the cavity. Caution had to be used because of an active lesion on the contralateral side. The sputum became negative in May, 1933, for nine months, and then, off and on, was Gaffky I or II on three different occasions until December, 1934. It has remained negative since that time. Patient has gained 54 lbs., is on exercise, and has developed normally along all physiological lines. X-ray on March 3,

Plate 1

For description of figures, see text under case I and case II.

1936, (figure 3, case II) showed an upper collapse of 90 per cent. The base was expanding, and at the level of the 2nd interspace was seen the scar where the cavity originally was. The contralateral lung showed fibrosis of the previously active lesion, with areas of calcification distributed throughout. This patient's lung is now being allowed to expand and she is in excellent condition. This case had been previously reported (31) and we present her here as under further observation.

III: C. M., a colored girl, 14 years old, admitted May, 1933. Briefly, her history was that about a month before entrance she developed dizziness and some shortness of breath while in school. She was sent home and remained there for two days. She went back to school and complained of sharp pain in her right side with a slight cough. It took two weeks before she was sent to a tuberculosis clinic, where her sputum was found to contain numerous tubercle bacilli. On entrance, May, 1933, (figure 1, case III) showed an extensive tuberculous pneumonia on the right side with a spilling over to the left. Fever 101° to 103°F. The patient was toxic, and her cough troublesome, with expectoration (Gaffky V). She was put on routine sanatorium care, with the hope that the lesion may have been of the type of an acute childhood infection. This was soon disproved (figure 2, case III), when the roentgeno-

Plate I

gram revealed a cavity, ¾ inch by 1¼ inch. The contralateral lesion showed progression and beginning excavation. Artificial pneumothorax was initiated on July 31, 1933, and progressive collapse was obtained. Fluid developed on the right side to a moderate degree, and within seven months the cavity was successfully collapsed. The sputum was converted to the negative stage within four months, but suddenly it turned positive again. Since the contralateral lesion progressed, we felt that the tubercle bacilli came from the left side. A roentgenogram (figure 3, case III), taken April 26, 1934, showed, on the right, the absorption of the fluid and disappearance of the cavity; but on the left there was a large cavity 1½ inches across. The right lung was allowed to reëxpand because we were not sure that it would do so, on account of the fluid, before we instituted artificial pneumothorax on the left. A roentgenogram (figure 4, case III), taken April 30, 1934, showed the right lung reexpanding, and 40 per cent collapse of left side. (Note the figure of eight cavities.) The patient's sputum became converted in June, 1934, when the cavities collapsed, and has remained so ever since. X-ray (figure 5, case III) on March 3, 1936, showed the right lung reëxpanded ,and the left under good compression, with disappearance of the cavities. The lower lobe on the left side was reëxpanding. The patient's fever, pulse and toxaemia disappeared within a couple of months after compression was started. She has gained 34 lbs. and is so far in very good condition.

IV: J. M., a white girl, 13 years of age, was admitted to the Sanatorium in July, 1934. She had been given a Mantoux test, which was strongly positive in July, 1933, when her brother was found to be an open case of tuberculosis. X-ray (figure 1, case IV) on July 14, 1933, showed the characteristic hilum involvement. About eight months later, she developed a cough with some expectoration. In another two months she had some blood-streaking of her sputum, and an X-ray (figure 2, case IV) on April 28, 1934, showed, on the right side, near the hilum, a cavity, 1 inch by 1 inch, with some perifocal infiltration. Her sputum showed Gaffky IV. She was immediately given artificial pneumothorax. Another roentgenogram on July 13, 1934, showed about 40 per cent collapse, with the cavity very evident. The girl developed a moderate amount of fluid, which we believe helped to close the cavity. A cavity near the hilum usually denotes a poor prognosis, but we succeeded in closing this cavity within five months. The patient's sputum was converted to a negative stage on August 18, 1934, and has remained so up to date. Another X-ray, on March 3, 1936, (figure 4, case IV) showed the complete disappearance of the cavity and some reëxpansion of the lung. At no time did this patient exhibit fever, toxaemia, or other signs of serious illness. To date she has gained 25 lbs. and she is in excellent condition.

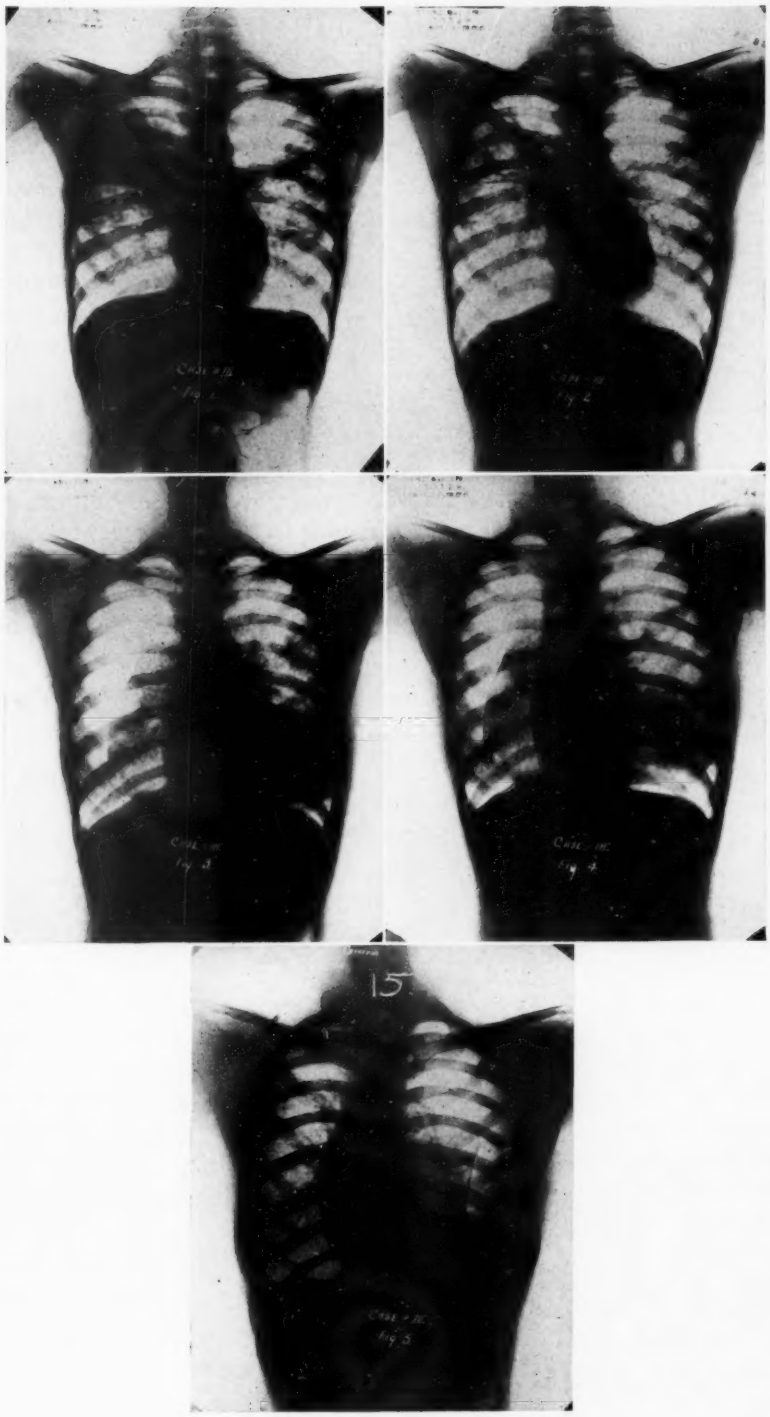

Plate 2

For description of figures, see text under case III.

V: D. G., a white girl, 14 years old, was admitted to the Sanatorium on April 30, 1935. Her history is interesting. Five years ago, she was routinely tuberculin-tested by Chadwick and his coworkers. She was found to have a 3-plus Mantoux test, besides X-ray evidence of childhood type of infection. She was sent to a preventorium at Plymouth, Massachusetts, where she remained for one year. Her people in the meantime moved to New Jersey. In January, 1935, she developed a slight cough without expectoration, but with loss of appetite. She had recurrent colds, and her mother became alarmed in spite of the family physician's assurance that the trouble was merely a "cold." The mother brought her daughter to the local tuberculosis clinic for examination. On entrance, the patient had no cough, expectoration or fever. Her loss in weight had been 10 lbs., even though, on entrance, she was above normal weight. A roentgenogram on entrance (figure 1, case V) showed marked involvement of the right upper lobe, with a cavity measuring $1\frac{1}{4}$ by $1\frac{1}{4}$ inches. Artificial pneumothorax was immediately instituted in spite of a persistently negative sputum and practically no symptomatology. The

Plate 3

For description of figures, see text under case IV and case V.

mother was rather anxious that we do pneumothorax. There was no history of contact. An X-ray on June 3, 1935 (figure 2, case V) showed a 60 per cent upper selective collapse and about a 30 per cent collapse of the other two lobes. The huge cavity is plainly visible. We succeeded in closing the cavity in about five months. A recent X-ray on March 3, 1936 (figure 3, case V) showed the successful compression of the cavity within a 90 per cent selective collapse. This patient has never had a positive sputum and has gained 19 lbs. since entry.

CONCLUSIONS

1. Juvenile patients do not fare well when harboring the adult type of tuberculosis. Tuberculosis still is the main cause of death in juvenile patients. The adult type of disease is responsible for the most of these deaths. Mere routine rest in bed, plus high vitamine diet has proved unsatisfactory in stemming this appalling death-rate.

2. Since prevention in most of the cases is impossible, we must be content in finding these cases as early as possible and institute some form of compression therapy suited to the case. If we are to find them early, we must closely observe the positive tuberculin cases by frequent roentgenographic follow-up. As soon as the adult disease appears, quick and

Plate 3

immediate compression therapy must be instituted in a properly equipped institution. The adult disease in juvenile cases is practically of the same type as seen in adults with the exception of some peculiar, unexplained reason that the juveniles do not seem to handle the disease as well.

3. The procedure of choice is artificial pneumothorax. Our best results have been obtained in those patients in whom a free pleural space could be found and this procedure applied and adequate collapse obtained.

4. If proper and adequate compression cannot be obtained, then an additional help must be offered, such as phrenic crushing. Phrenic crushing is a valuable addition in those cases in which adhesions prevent proper therapeutic collapse.

5. Phrenic crushing, done alone in selected cases, can be successful, provided it is not done in every case in which a free pleural space cannot be obtained. Even in the latter cases, phrenic crushing may help to rest the lung to some extent. Of course, most of our disappointing results were in the latter cases. We cannot blame the procedure, because the cases are usually in the advanced stage, but we feel that something should be done. If the procedure has not done anything but prolong life and give some comfort to the patient, we should be satisfied. No doubt, in some cases, the lesion becomes progressive and, no matter what method of compression is applied, the case will progress to a fatal termination.

6. Pneumolysis can be utilized in children in selected cases. We have not had enough cases to be able to tell of its merits. Since this procedure is successful in certain cases in adults, we cannot see why the same results cannot be obtained in juvenile patients.

7. We have not had any thoracoplasty work performed on juvenile patients. We have at present two cases that have had a phrenic crushing without any apparent changes. A certain amount of courage and forethought will, however, be necessary before thoracoplasty can be considered. The surgeons are even hesitant, but it is our opinion that some of these children should have the benefit of this procedure. We lost a case two years ago when pneumothorax and phrenic crushing did not improve the patient after a year of intensive therapy. If thoracoplasty had been performed, that patient may have lived, and perhaps be well.

8. The aim of those doing compression therapy, especially artificial pneumothorax, should be for an optimum compression, conducive to successful collapse of the diseased lung. One should not hesitate to do

bilateral artificial pneumothorax if indicated. These patients are generally in need of such procedures, and the outlook without compression is, indeed, doubtful.

9. Children having positive sputum should be separated from those having negative sputum. We believe that, in some cases, cross-infection can and does occur.

10. Forty-nine children, between the ages of 5½ and 15 years, received active therapeutic collapse for periods of from 6 months to 5 years. In this series, 9 died, most of them during the early period of our work. In 3 cases the outlook is not good, and in 2 others it is fair, but it is too early to foretell the outcome. The latter should have thoracoplastic operations if sufficient courage can be summoned.

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TUBERCULOUS PNEUMONIA AND DIABETES MELLITUS

Report of a Case Treated With Artificial Pneumothorax and Insulin With Marked Improvement[1,2]

H. CLARE SHEPARDSON AND C. A. NOBLE, JR.

Tuberculous pneumonia is, of itself, a serious disease. When, however, it occurs in a patient already ill with moderately severe diabetes, the prognosis is considered extremely grave. Rarely, however, recoveries occur. In these latter cases, it is apparently the meticulous treatment of the tuberculous infection as well as adequate control of the diabetes that bring about the more fortunate outcome. Perfect cooperation is essential, and every necessary detail in the treatment of both the tuberculosis and the diabetes must be personally supervised.

For three years, a patient suffering from this combination of diseases has been under observation.[3] Her recovery and almost complete rehabilitation would seem a sufficient reason for this case-report.

Z. J., single, registered nurse, 34 years of age, entered the University of California Hospital, March 13, 1933, in ketosis. *Family history* of diabetes or tuberculosis negative. *Past history* of influenza and smallpox, accompanied by a marked albuminuria, together with definite uraemia, with, however, satisfactory recovery, in 1922. Appendiceal abscess drained and a right salpingoöphorectomy done in 1927, at which time urine was negative for sugar.

During summer of 1928, patient began to notice polydypsia, polyphagia, weakness, irritability, blurring of vision, and pruritis vulvae. Lost weight for two months at rate of about a half-pound daily. Diagnosis of diabetes mellitus made, and patient was put on qualitatively restricted diet, together with 28 units of insulin daily. Although usually aglycosuric, routine examinations of urine would occasionally reveal complete reduction of Benedict's solution. In 1929, a year later, during an attack of bronchitis, was thor-

[1] From the Department of Medicine, University of California Medical School, San Francisco, California.

[2] Read at the annual meeting of the California Tuberculosis Association, Sacramento, California, April 3, 1936.

[3] Throughout her acute illness this patient was under the observation of Dr. Sidney Shipman of San Francisco. His care in treating the tuberculosis, together with his considerate coöperation with the authors in the management of the patient's severe diabetes, is largely responsible for the favorable outcome.

oughly examined by competent physician: no physical signs of tuberculosis. A chest film taken then, was said to show no evidence of tuberculosis although unfortunately the film has since been lost. In 1932, had attack of diabetic coma sufficiently severe to require 175 units of insulin in first 24 hours. It was on the second day of this episode that patient first came under care of one of us (H. C. S.). After recovering from coma, was placed on weighed diet (CHO. 140 gm., P. 80 gm., F. 120 gm., calories 1960), with 30 units of insulin before breakfast and 15 units before supper. Adhered fairly well to diet, gained slightly (from 136½ to 145 lbs.), and was entirely symptom-free except for occasional mild insulin reactions.

Patient's acute illness began February 18, 1933, when she developed fever, night-sweats and cough, thought to be an attack of influenza. Being a nurse, patient felt herself competent to care for her own illness and failed to call a physician. As result, was not seen until March 13, 1933, when she was found to have not only severe cough but fever of 38.9°C. At this time urine contained large amount of acetone as well as sugar. Given 20 units of insulin immediately, and sent to University Hospital, which she entered at 9:00 P.M. By 11:00 P.M., after 45 units of insulin had been administered, her blood sugar was 80 mgm. per cent and CO_2-combining power 42 vol. per cent. At time of entry, patient obviously toxic and apathetic, with signs of consolidation over entire upper lobe of right lung. Had slight anaemia, and moderate elevation of leucocytes. Differential count was normal. (Hgb. 78 per cent (Sahli); rbc 3,890,000; wbc 12,000; neutrophiles 78 per cent.) Sedimentation time 20 minutes. Urine, in addition to sugar and acetone, had faint trace of albumin and innumerable leucocytes. Sputum showed many tubercle bacilli. Bedside chest film showed shrinking of right upper lobe, with marked uniform increase in density in right upper pulmonary field except for circular area which was entirely clear (figure 1). Findings interpreted by Dr. R. S. Stone as tuberculosis of sufficiently long standing to cause contraction of lobe with formation of two cavities, and, in addition, probably pneumonia. Clinically, tuberculous pneumonia was definite.

Patient's subsequent course can best be followed by chart 1 and table 1. Two days after admission, in spite of constant observation, she developed diabetic coma. Although clinically she was only slightly drowsy, the CO_2-combining power of her blood sank to 17 vol. per cent. Again she responded rapidly to the additional insulin administered.

Artificial pneumothorax first induced on March 17th. Has been maintained, not only during hospital stay, but to present time. Only two reactions following introduction of air: both mild; as shown on chart, on March 30th and April 13th, fever rose one to two degrees, these being "pneumothorax days."

Control of diabetes particularly difficult in early stages of patient's acute

illness, due to marked variation in food intake (see chart 1). This inability to maintain constant caloric intake increased markedly tendency to insulin reactions, of which the patient had many, some of them quite severe: Once, her blood sugar dropped to 50 mgm. per cent. Another feature, frequently

Fig. 1. Bedside film of chest, taken March 14, 1933, the day after patient's admission with severe diabetes and tuberculosis. There is shrinking of the right upper lobe, and uniform increase in density of the right upper pulmonary field, which, however, contains two cavities.

seen in diabetic patients with severe infections and very strikingly illustrated in this case, was extreme rapidity with which ketone bodies appeared in the urine with the least glycosuria. That this phenomenon has not persisted since she has become afebrile suggests that the toxicity and fever were in part at least responsible for the lability in ketone production.

TABLE 1

Tuberculous pneumonia and diabetes mellitus

This is a summary of the patient's diabetic record extending over a period of three years. The instability of diabetes in the presence of an active infection is well illustrated

DATE	DIET				INSULIN	WEIGHT	URINE* (REDUCTION OF BENEDICT'S QUAL. SOLUTION)				URINE ACETONE	BLOOD SUGAR	OTHER DATA
	C.	P.	F.	Cal.			1	2	3	4			
					units								
2/21/32								+++	+++	++	++		
2/22/32	100	50	30	870	25–20–25–0		+++	+	0	+			
2/23/32	100	70	50	1130	25–20–25–0	136½	+	0	+++	0	0	125	1½ hr. p.c.
2/24/32	100	70	50	1130	35–20–20–3		0	0	++	0			
2/25/32	120	70	100	1660	25–10–20–3	135	0	0	0	0			
2/29/32	130	70	120	1880	25–0–20	135	+++	0	+	0			Reactions at night
4/11/32	140	80	120	1960	30–0–15	131¾	+++	+	0	0		362	1½ hr. p. c.
9/ 8/32	120	75	140	2040	45–0–15	137½	+	+	+	+++			
12/17/32	120	75	140	2040	45–0–20	141	0	0	0	0		228	1½ hr. p. c.
2/27/33	120	75	140	2040			+++	0	0	+++			
					Patient admitted to University of California Hospital, 3–13–33. For further record see chart 1								
4/12/33	238	80	150	2892	25–20–0–20		+	0	0	++++	+	148	
4/13/33	238	80	150	2892	30–15–20–0		+	0	0	+++	0		
4/14/33	238	80	150	2892	30–15–15–25		0	0	0	+++	+		
4/15/33	238	80	150	2892	30–15–15–0		0	0	0	++++			
4/16/33	238	80	150	2892	30–25–15–10–0–25		++++	+	0	+			
4/17/33	238	80	150	2892	30–35–10–25		+	0	0	+			
4/18/33	238	80	150	2892	30–15–15–25		0	0	0	0			
5/17/33	282	80	200	3248	25–10–10–25		0	0	0	0			
5/18/33	282	80	200	3248	25–10–10–25		+	+	+	0			
5/19/33	282	80	200	3248	25–5–15–20–10		+	++	+	0	0		Insulin reaction
5/20/33	282	80	200	3248	25–10–10–25		0	0	+	0			
5/24/33	282	80	200	3248	20–10–10–20	125	0	0	0	0			

Patient discharged from University of California Hospital, 5–25–33

2/ 2/34	175	80	165	2505	18–8–8–6	158½	0	0	0	0		060	4 hr. p. c.
8/21/34	150	80	165	2405	24–6–6–8	152¼	+++	++	+	+			
9/17/34	150	80	165	2405	30–4–6–12	153¾	+++	+	0	+++			
11/13/34	150	80	165	2405	30–0–10–14	152¾	+	0	+	+			
3/12/35	150	80	150	2270	30–0–10–6	150½	+++	0	+++	+++			
4/ 4/35	150	80	150	2270	30–0–17–12	150½	+++	+++	+	+	0		
5/ 2/35	150	80	150	2270	30–0–15–12	152¼	+	+	+	+++		073	a. c.
												135	1½ hr. p. c.

* 1. Urine voided between breakfast and lunch.
2. Urine voided between lunch and dinner.
3. Urine voided between dinner and bedtime.
4. Urine voided between bedtime and breakfast.

Marked improvement in cough followed immediately after inducing pneumothorax, although amount of sputum varied little. However, the patient remained critically ill for three weeks. Then, rather abruptly, definite improvement occurred. She became more alert, began to eat better, and, although her caloric intake had been maintained at a high level most of the time,

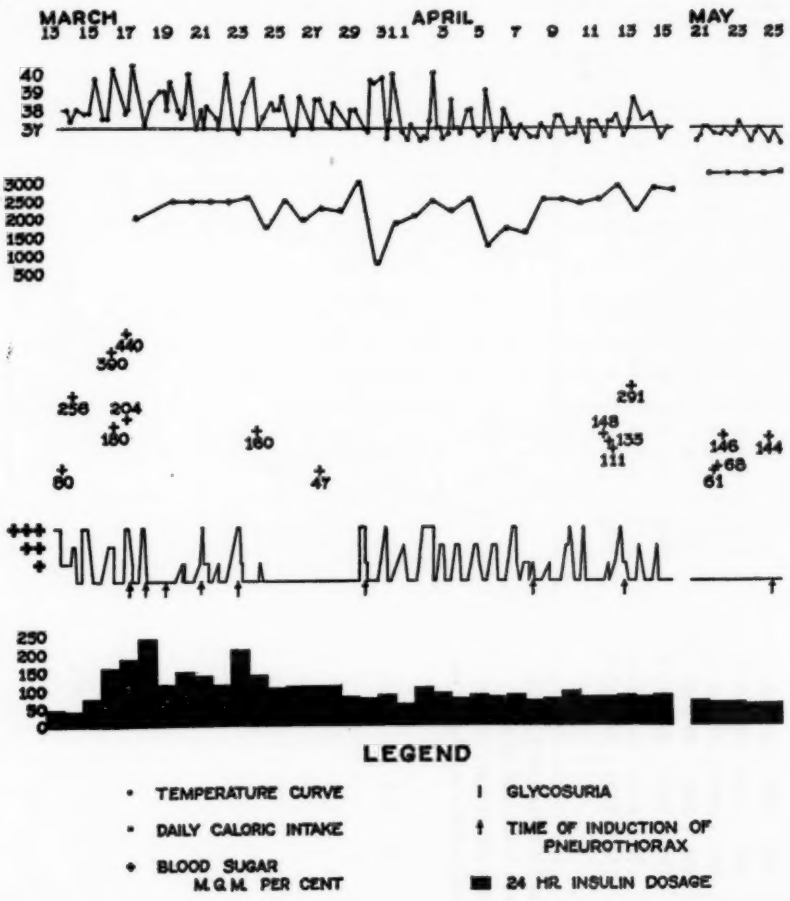

CHART 1

her appetite increased and she became interested in food. From then on, her fever gradually subsided, and the temperature was completely normal at discharge, May 25, 1933. One month after entry, her sputum became free from tubercle bacilli and has remained so.

On leaving the University Hospital, the patient was transferred to the Ross

Sanitarium, since when we are indebted, for records, to Dr. Sidney Shipman under whose care she has been. On admission to that institution she weighed 128 lbs.; on discharge, December 4, 1933, 165 lbs. A diet of 2,500 calories or more had been maintained. In spite of this high caloric intake, gradual reduction in the insulin dosage from 60 to 42 units daily was possible. Except for a rise in temperature to 37.3°C. on one occasion the patient has continued to be afebrile. From July, 1934, to the present she has been up and about 12 hours daily and has been able to resume her duties as a nurse. The pneumothorax is maintained by injections every three to four weeks. Although the diabetes is quite well controlled, the urine does not remain entirely sugar-free. This sporadic glycosuria in all probability results from occasional dietary indiscretions. However, the blood sugar remains within very satisfactory limits, varying from 73 to 135 mgm. per cent.

DISCUSSION

The association of pulmonary tuberculosis and diabetes mellitus was first described by Richard Morton (1) in 1694. Since then there has been a growing and voluminous literature on the subject, leading up to the recent excellent and most complete summary by Root (2). A short discussion of the more significant points in this combination of diseases seems all that is warranted in this brief report.

The consensus of opinion indicates that when the two diseases coexist the onset of the tuberculosis follows that of the diabetes in a large proportion (85 per cent in Root's series) of cases (3). The history of our patient clearly establishes the fact that her diabetes began in 1928. One year later, examination of the chest and roentgenographic studies were quite negative for tuberculosis. Symptoms of tuberculosis did not begin until 1933—five years later—but films of the chest showed retraction of the lung at the right apex. Evidence that adhesions had formed, demonstrated during therapy with artificial pneumothorax, likewise indicated that the active process had existed for some time before the onset of the patient's acute febrile illness.

Is the incidence of tuberculosis greater among individuals with diabetes than in the general population? In the last century statistics show that, in some series, as many as 50 per cent of diabetic patients died of pulmonary tuberculosis (4). More recent figures seem to indicate that at the present time the actual percentage of active tuberculosis found in diabetic patients at autopsy only slightly exceeds that in the general population. Root's data, compiled from a literature covering 51,705 autopsies, showed active tuberculosis present in 22.9 per cent of non-

diabetic individuals, a figure which corresponds fairly closely with the 28.4 per cent occurrence in his series of 1,191 autopsies of diabetic patients. However, as Carlson and Bell (5) have suggested, a patient usually dies of only one major disease; consequently, even though autopsy statistics should indicate that the diseases occurred together with no greater frequency than that of the incidence of tuberculosis in non-diabetics, this would indicate a real incidence two to three times as great. Moreover, in comparing mortality rates of tuberculosis and diabetes, one must realize the difference in the average age at death from the two diseases. In 1928, 81 per cent of the deaths from tuberculosis (U. S. Census) occurred before the age of 45, while 60 per cent of all diabetes begins after the age of 40. This age difference still further emphasizes the fact that the patient with diabetes is more susceptible to tuberculosis than the patient not so afflicted. If one follows the association of tuberculosis and diabetes further, one finds that, while the morbidity and mortality of tuberculosis, in this country at least, are definitely on the wane, the mortality from diabetes alone is clearly rising. Furthermore, since the advent of insulin, the average length of life of the diabetic individual has increased. There is, therefore, definitely a longer period of time in which to develop tuberculosis. In addition, the more widespread use of roentgen-ray examinations has enabled the clinician to diagnose the presence of tuberculosis at an earlier stage in its development. As a result, treatment, which likewise has improved considerably in the past decade, is instituted sooner. Consequently, the patient with both tuberculosis and diabetes lives longer than formerly, just as does the individual who has either tuberculosis or diabetes uncomplicated by the other disease.

One predisposing factor in the development of tuberculosis is probably the occurrence of severe acidosis. Root (2) makes the significant statement that the incidence of coma among tuberculous diabetics is five times that in the general diabetic population. In our patient there is a clear story of coma occurring one year prior to the onset of her symptoms of active tuberculosis.

When tuberculosis does occur in the diabetic patient, the exudative type seems to be unusually common. Naunyn (6) called attention to this fact in recording the tendency to caseation and rapid breakdown in such patients. Sosman and Steidl (7), in a group of 182 consecutive diabetic patients, found 45 with roentgen evidence of tuberculosis, of which 21 cases had a bronchopneumonic form, the disease localizing

about the hilum. These findings suggested to them the form of tuberculosis so often seen in childhood, although all but three of their patients were over 45 years of age. These writers named this syndrome "diabetic tuberculosis." Wiener and Kavee (8), in a review of 26 diabetic patients with tuberculosis, confirmed the statement that the lesions were mainly of the "diabetic type,"—the soft exudative form found more commonly in the middle zone accompanied by very rapid caseation and liquefaction. Fishberg (9), as well as Rosenberg and Wolf (10), Banyai (11), and others, also reported the exudative form of the disease as occurring more commonly in diabetic patients, but found no predominance of the hilar form. Root (2) found caseous pneumonia in nine of 55 cases of tuberculosis in diabetic patients, while in a larger series of 89 he reports only 16 cases of the pure hilar disease as described by Sosman (7). On the other hand, Lorenzen (12), in his group of 143 cases, found all forms of tuberculosis; he felt, moreover, that those patients with severe diabetes had a greater tendency to develop the exudative type, whereas those with milder diabetes seemed to develop a fibrotic type of the disease. Curschmann (4), as well as Myers and McKean (13), also believes that no form of tuberculosis is typical of diabetes. Kramer and Lawson (14) found no case of hilum tuberculosis in 408 roentgen-ray examinations of 500 diabetic patients.

In the patient here presented the disease was predominantly exudative, with rapid onset, but was apical rather than hilar in location. Root (2) distinguishes such acutely developing pneumonia, with marked toxicity, from the cases without toxic symptoms but with radiological evidence of bronchopneumonic infiltration. Other authors fail to make this distinction; from the literature a statistical study of the frequency of tuberculous pneumonia, therefore, is not possible.

Most authors feel that tuberculosis, particularly the exudative type, aggravates the diabetes, especially during the active stage of the former disease (3) (6) (15). With this opinion we are in accord, for, while there may be apparent a transitory increase in tolerance largely because of the poor appetite of the patient, subsequent developments usually bring about a definite though usually temporary increase in the severity of the diabetes. Occasionally there is an absolute loss of tolerance, which is not regained when the patient becomes afebrile and which is not accounted for by the usually greatly increased food intake. There is no confirmation of the work of Lundberg (16), who suggested that tuberculous tissues supply an insulin-like substance capable of producing an

actual rise in sugar tolerance in tuberculous diabetic patients. During the febrile course of her disease, the tolerance of our patient dropped markedly, so that 154 units of insulin were required for her to metabolize 231 gm. of available carbohydrate. When, however, she became afebrile, her tolerance again rose, so that only 70 units of insulin were necessary in spite of the fact that she was getting a diet with a glucose equivalent of 345 gm.; furthermore, during this period she was absolutely inactive. At present, with moderate activity, she needs 57 units of insulin to utilize adequately 210 gm. of effective carbohydrate.

Root and others mention the frequent tendency of tuberculosis, when present in the diabetic patient, to progress without symptoms or signs. In those cases in which the disease is localized around the hilum, this would, of course, tend to be true. In older people, too, physical signs and symptoms are likely to be less definite (10).

TREATMENT

In the days before insulin was available, the treatment of diabetes was diametrically opposed to that of tuberculosis. Tuberculous patients were given high-caloric forced feedings, while diabetic patients were starved. When insulin came into general use, it was felt that this would provide a means of maintaining nutrition in spite of the presence of diabetes. Very soon, however, reports were published, stating that there was grave danger of lighting up old foci of tuberculosis, of causing rapid progression of an existing disease, and of increasing fever. They emphasized the serious consequences of producing severe insulin reactions (17). Fishberg (9), especially, adopted this point of view. As a result, he advocated the use of insulin in tuberculous diabetic patients only as a life-saving remedy, and Myers and McKean (13) cite three cases in which insulin reactions seemingly hastened death. However, most writers now feel that the danger attributed to the giving of insulin was exaggerated and that impurities in insulin in the earlier days may have been responsible for the reported severe reactions. Moreover, tuberculous patients with diabetes are subject to rapid changes in condition even without insulin. Delijannis and Petassis (18) in Falta's clinic think that insulin furnishes a means of improving the resistance of diabetic patients to tuberculosis, by increasing their appetites, and consequently their state of nutrition. They therefore suggest that diabetic patients having tuberculosis should be treated with insulin. Root mentions that the toxic symptoms of tuberculosis have an unfavorable influ-

ence on the diabetic tolerance and that during insulin treatment reactions are common. Apparently the patient's susceptibility to insulin is increased, for Root cites one case with tuberculous pneumonia in which 15 units of insulin reduced the blood sugar from 420 to 40 mgm per cent. He feels, however, that the length of life of such patients has undoubtedly been increased by the use of insulin. Also, Kutschera-Aichbergen (15) cites three cases of exudative tuberculosis with pneumonia which were improved by insulin together with a high carbohydrate diet.

Hart and Creel (19), in 1919, treated a tuberculous diabetic patient with pneumothorax, and later, in 1922, with insulin. Laignel-Levastine (20) and co-workers in 1923 also observed one patient who improved when treated with a combination of pneumothorax and insulin; and LeNoir and Sherrer (21) likewise cite one patient similarly treated with marked improvement. Blum (22) reported a case of severe diabetes and tuberculosis in which pneumothorax and adequate insulin therapy were maintained for four years with progressive improvement. Wiener and Kavee (8) report 26 cases in which pueumothorax was used together with insulin, and note marked improvement in nine. In three cases the use of air seemed to reduce the insulin requirement. The degree of collapse obtainable is apparently important. In our patient it is significant that, except for a few adhesions at the apex, a complete collapse has been maintained for more than two years.

PROGNOSIS

That tuberculosis has always been considered a serious complication of diabetes is attested by some of the following figures. Lorenzen (12) reported 116 deaths among 143 cases of tuberculosis in diabetic patients from 1918 to 1931, with almost all cases dying in the first three years. Gotten (23) reports a mortality of over 50 per cent in one year. Rosenberg (10) mentions caseous pneumonia in a group of cases in which he felt that there was an utterly bad prognosis. But he cites the case of one patient with caseous pneumonia of the right lower lobe who has improved and is living one and one-half years later, although this improvement itself had caused him to doubt the diagnosis. Since the use of insulin, however, the prognosis of the tuberculous diabetic patient has been much better, in spite of the fact that Sosman reports a uniformly bad prognosis as late as 1927, even with insulin. In fact, Myers and McKean suggest that the tuberculous patient with diabetes, as long as the latter disease is controlled, may improve even more rapidly than the

patient with tuberculosis alone, since the relatively lower carbohydrate intake and proportionately higher fat consumption induce less active pulmonary ventilation.

A few patients with proved tuberculous pneumonia have been returned to useful lives. Our patient adds another to this rather limited group. But with the more widespread use of high caloric diets, insulin, pneumothorax and rest, it is to be hoped that diabetic individuals who develop tuberculosis may attain the rapidly increasing longevity of those patients having either tuberculosis or diabetes alone.

SUMMARY

1. Tuberculosis occurs two to three times as commonly in individuals with diabetes as it does in the general population, and the combination of the two diseases is on the increase.

2. When the diseases coexist, the diabetes usually precedes the tuberculosis.

3. The exudative type of tuberculosis is unusually common in tuberculous diabetic patients.

4. Tuberculous pneumonia was formerly of uniformly bad prognostic import.

5. Pulmonary tuberculosis frequently occurs in diabetic patients after coma.

6. Tuberculosis increases the severity of diabetes, and consequently makes the latter disease more difficult to control.

7. Tuberculous diabetic patients can tolerate safely, and should be given insulin, to enable them to maintain a satisfactory state of nutrition.

8. Frequent insulin reactions are to be expected.

9. Artificial pneumothorax is of value. The indications for the use of this procedure in the diabetic patient with tuberculosis are similar to those in the nondiabetic.

10. A case is reported, in which a patient with tuberculous pneumonia and diabetes has recovered sufficiently to return to work.

11. In view of the susceptibility of the diabetic population to tuberculosis, all persons having diabetes should be subjected to roentgen examinations and to frequent physical examinations of their lungs.

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TUBERCULOSIS AND MALIGNANT TUMORS

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This study, concerning the incidence and relation of tuberculosis and malignant tumors in the same individual as seen at necropsy, was initiated by the various contradictory statements that have appeared in a rather voluminous literature during the past few years. It has been pointed out by Pearl (1) that tuberculosis and malignant tumor are antagonistic and rarely occur actively and concomitantly in the same individual. Some believe that one favors the other, while a few maintain that the incidence and progress of these conditions are independent. Wilson and Maher (2) have proved that Pearl's thesis is erroneous, but they are undecided as to whether any degree of positive association exists between the two diseases.

This report is presented, not with the hope of ending the controversy, but as an effort to add further accumulating knowledge concerning the question. Its purpose will have been well served if the report here rendered stimulates others to an unbiased study from which more definite conclusions may be made.

SOURCE OF MATERIAL

The material for this study was obtained from the protocols of 2,000 consecutive necropsies[3] on members of the white and black races, one year of age and older, performed by members of the Department of Pathology of the University of Tennessee during the period January 1, 1922, through September 18, 1935. Most of the cases were admitted to the John Gaston Hospital, although a few were referred by physicians from their private practices.

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[3] A necropsy was considered acceptable for this study if the viscera of both the thoracic and abdominal cavities were examined, it being considered unnecessary to examine the cranial contents in each case.

METHOD OF STUDY

The cases were divided into three major groups: (1) malignant tumors, (2) tuberculosis, and (3) a miscellaneous group in which there was no evidence of these two conditions. There was some overlapping in the first two groups due to the presence of both diseases in the same individual. These three groups were classified according to race, sex and two age-groups: (1) from 1 to 34 years, and (2) those 35 years of age and older. This age division was chosen because the latter group is considered the "cancer age" notwithstanding the fact that malignant tumors other than of carcinomatous nature are included in this report. Comparisons were made between the various groups.

In this study one or more of the following pathological tissue criteria were made use of in the classification of cases: (1) in tuberculosis, the proliferative and/or exudative reaction as described by MacCallum (3), and caseation necrosis; and (2) in the malignant tumors, a definite picture of malignancy in the primary tumor, tumor-cell emboli in lymph- or blood-vessels, and metastases in the regional lymph nodes and/or the lungs or liver. All but a few cases were examined histologically.

RESULT OF STUDY

1: General incidence and relation: Without regard to race, sex or age-groups, the 2,000 cases were divisible into three general incidence groups as follows:

	Number of cases	*Per cent*
Malignant tumor	131	6.55
Tuberculosis	480	24.00
Others*	1,410	70.50
	2,021	101.05
Cases counted twice	21	1.05
	2,000	100.00

* Those cases showing no evidence of tuberculosis or a malignant tumor. This term is used with the same significance in other tables.

The cases counted twice indicate the total number of cases in which both tuberculosis and a malignant tumor existed: thus, only 21 (1.05 per cent) at necropsy showed evidence of both diseases. If a comparison is made between this double-lesion group and the total number of cases in each of the two disease groups, it is found that 4.37 per cent of all people with tuberculosis also have a malignant tumor, while 16.03 per cent of all people with a malignant tumor also have tuberculosis.

Therefore, while the incidence of the double-lesion group as compared to the total number of necropsies is relatively low, the incidence assumes greater importance when compared with the two disease groups in question.

2: Race incidence and relation: In the total number of cases there were 543 members of the white race (27.15 per cent) and 1,457 members of the black or Negro race (72.85 per cent), classifiable as follows:

	Whites		*Blacks*	
	Number of cases	*Per cent*	*Number of cases*	*Per cent*
Malignant tumor	42	7.73	89	6.11
Tuberculosis	120	22.10	360	24.71
Others	390	71.82	1,020	70.00
	552	101.65	1,469	100.82
Cases counted twice	9	1.65	12	0.82
	543	100.00	1,457	100.00

Thus it is evident that the incidence of the double-lesion group, as well as that of malignant tumor in general, is somewhat higher in the white than in the black race; whereas, the incidence of tuberculosis is greater in the Negro. The incidence of the double-lesion group in each race-group, as compared with the total number of tuberculous cases and malignant tumors, is: (1) 7.50 per cent of the white race with tuberculosis also have a malignant tumor, while 21.42 per cent of white people with a malignant tumor also have tuberculosis; whereas (2) only 3.33 per cent of tuberculous Negroes have a malignant tumor, and 13.48 per cent of the Negro race with a malignant tumor also have tuberculosis.

3: Sex incidence and relation: In the total number of cases there were 1,367 males (68.35 per cent) and 633 females (31.65 per cent), classifiable as follows:

	Males		*Females*	
	Number of cases	*Per cent*	*Number of cases*	*Per cent*
Malignant tumor	85	6.21	46	7.27
Tuberculosis	322	23.56	158	24.96
Others	972	71.10	438	69.19
	1,379	100.87	642	101.42
Cases counted twice	12	0.87	9	1.42
	1,367	100.00	633	100.00

From this comparison the following data are obtained: (1) the incidence of tuberculosis and a malignant tumor, each as an entity, is somewhat

higher in the female than in the male; consequently (2) the incidence of the double-lesion group is greater in the female (1.42 per cent) than in the male (0.87 per cent). The incidence of the double-lesion group in each sex, as compared with the total number of tuberculous cases and malignant tumors, is :(1) 3.72 per cent of all tuberculous males also have a malignant tumor, while 14.11 per cent of all males with a malignant tumor also have tuberculosis; whereas (2) 5.69 per cent of tuberculous females also have a malignant tumor, and 19.56 per cent of females with a malignant tumor also have tuberculosis.

4: Age incidence and relation: The total number of cases was divisible into two age-groups: (1) from 1 to 34 years, containing 825 cases (41.25 per cent); and (2) 35 years of age and older, 1,175 cases (58.75 per cent), classifiable as follows:

	1 to 34 years		*35 years plus*	
	Number of cases	*Per cent*	*Number of cases*	*Per cent*
Malignant tumor	25	3.03	106	9.01
Tuberculosis	242	29.33	238	20.26
Others	562	68.12	848	72.17
	829	100.48	1,192	101.44
Cases counted twice	4	0.48	17	1.44
	825	100.00	1,175	100.00

From this comparison the following data are obtained: (1) the incidence of malignant tumor is approximately three times as great in the older age-group; (2) tuberculosis is found more frequently in the younger age-group; (3) the incidence of tuberculosis and malignant tumor, each as an entity, is appreciably greater in the younger group (31.88 per cent) than in the older group (27.83 per cent); whereas (4) the incidence of the double-lesion group is highest in the second age-group. The incidence of the double-lesion group in each of the age-groups, compared with the total number of persons with tuberculosis and malignant tumor, is: (1) 1.65 per cent of those in the younger age-group who have tuberculosis also have a malignant tumor, while 16.00 per cent of those having a malignant tumor also have tuberculosis; whereas (3) 7.10 per cent of those in the second age-group having tuberculosis also have a malignant tumor, and 16.03 per cent who have a malignant tumor also have tuberculosis.

5: Race-sex incidence and relation: If the total number of whites and blacks are subdivided into sex-groups: (1) white males, 370 cases; (2) white females, 173 cases; (3) black males, 997 cases; and (4) black fe-

males, 460 cases, and compared as in the previous groups, the following data are obtained:

	Males		Females	
Whites	*Number of cases*	*Per cent*	*Number of cases*	*Per cent*
Malignant tumor	28	7.66	14	8.09
Tuberculosis	85	22.97	35	20.23
Others	264	71.35	126	72.83
	377	101.88	175	101.15
Cases counted twice	7	1.88	2	1.15
	370	100.00	173	100.00
Blacks				
Malignant tumor	57	5.72	32	6.95
Tuberculosis	237	23.77	123	26.74
Others	708	71.01	312	67.83
	1,002	100.50	467	101.52
Cases counted twice	5	0.50	7	1.52
	997	100.00	460	100.00

Thus, it is found (1) the incidence of malignant tumor is appreciably higher in the white female than in any other race-sex group; (2) tuberculosis occurs most frequently in the black female; (3) the incidence of tuberculosis and malignant tumor, each as an entity, is greatest in the black female (32.17 per cent) and lowest in the white female (27.17 per cent); whereas (4) the incidence of the double-lesion group is greatest in the white male (1.88 per cent) and lowest in the black male (0.50 per cent). The incidence of the double-lesion group in regard to the total number of cases of tuberculosis and malignant tumor in each race-sex group is:

Tuberculosis-malignant tumor group

	Number of cases	*Malignant tumor Per cent*	*Tuberculosis Per cent*
(1) White males	7	25.00	8.23
(2) White females	2	14.28	5.71
(3) Black males	5	8.77	2.10
(4) Black females	7	21.87	5.69

It is surprising to note the high incidence (25.00 per cent) of white males with malignant tumor who also have tuberculosis, approximated only by the same double-lesion (21.87 per cent) in the black female, while the lowest incidence occurs in the black male (8.77 per cent). The incidence of tuberculosis among people with malignant tumor is

approximately three to four times as great as is malignant tumor occurring among the tuberculous in each race-sex group.

6: Race-sex-age incidence and relation: If the race-sex groups are subdivided according to age: (1) white males of 1 to 34 years, 107 cases; (2) white males of 35 years plus, 263 cases; (3) white females of 1 to 34 years, 100 cases; (4) white females of 35 years plus, 73 cases; (5) black males of 1 to 34 years, 378 cases; (6) black males of 35 years plus, 619 cases; (7) black females of 1 to 34 years, 240 cases; and (8) black females of 35 years plus, 220 cases; and compared with each other, the following information is obtained:

(1) White males

	1 to 34 years		*35 years plus*	
	Number of cases	*Per cent*	*Number of cases*	*Per cent*
Malignant tumor	4	3.73	24	9.12
Tuberculosis	21	19.62	64	24.34
Others	83	77.57	181	68.82
	108	100.92	269	102.28
Cases counted twice	1	0.92	6	2.28
	107	100.00	263	100.00

(2) White females

Malignant tumor	2	2.00	12	16.44
Tuberculosis	21	21.00	14	19.17
Others	77	77.00	49	67.12
	100	100.00	75	102.73
Cases counted twice	0	0.00	2	2.73
	100	100.00	73	100.00

(3) Black males

Malignant tumor	10	2.65	47	7.59
Tuberculosis	121	32.01	116	18.74
Others	248	65.60	460	74.31
	379	100.26	623	100.64
Cases counted twice	1	0.26	4	0.64
	378	100.00	619	100.00

(4) Black females

Malignant tumor	9	3.75	23	10.45
Tuberculosis	79	32.91	44	20.00
Others	154	64.17	158	71.82
	242	100.83	225	102.27
Cases counted twice	2	0.83	5	2.27
	240	100.00	220	100.00

Thus, it is found (1) that the incidence of malignant tumor is considerably higher (16.44 per cent) in the oldest white female group than any other race-sex-age group, and approximated only by an incidence of 10.45 per cent in the corresponding black female group; (2) that tuberculosis has its highest incidence in the younger black female and male groups (32.91 per cent and 32.01 per cent, respectively); (3) that the incidence of tuberculosis and malignant tumor, each as an entity, is greatest in the black female 1 to 34 years of age (35.83 per cent); whereas (4) the incidence of the double-lesion group is greatest in the white female 35 years of age and older (2.73 per cent). The incidence of the double-lesion group in regard to the total number of cases of tuberculosis and malignant tumor in each race-sex-age group is:

Tuberculosis-malignant tumor group

	Number of cases	Malignant tumor Per cent	Tuberculosis Per cent
(1) to 34 years			
White males	1	25.00	4.76
White females	0	.....	....
Black males	1	10.00	0.82
Black females	2	22.22	2.53
(2) 35 years plus			
White males	6	25.00	9.37
White females	2	16.66	14.28
Black males	4	8.51	3.44
Black females	5	21.73	11.36

As is to be expected from previous calculations, the incidence of tuberculosis among people with malignant tumor is greatest (25.00 per cent) in the white male of each age-group while the lowest incidence occurs in the black male of the second age-group (8.51 per cent), with the exception of the youngest white female group in which a double-lesion did not occur in a total of 100 cases.

7: Specific malignant tumor-tuberculosis combinations: All previous calculations have been based on the total number of malignant tumors without regard to their several types. The 131 cases of malignant tumor are divisible into 6 general groups: (1) carcinoma, 105 cases; (2) sarcoma, 11 cases; (3) hypernephroma, 7 cases; (4) malignant glioma, 4 cases; (5) mesothelioma, 3 cases; and (6) haemangioendothelioma, 1 case.

Tuberculosis was found associated with carcinoma in 16 instances (15.23 per cent) as follows:

1: Gastric carcinoma with metastases to regional lymph nodes; tuberculosis of right lung; white male, aged 65, A-3189.
2: Gastric carcinoma without metastases; tuberculosis of stomach, lungs and tracheobronchial lymph nodes; white male, aged 63, A-2517.
3: Gastric carcinoma with metastases to liver; tuberculosis of lungs and tracheobronchial lymph nodes; white male, aged 55, A-462.
4: Gastric carcinoma with metastases to regional lymph nodes, liver, spleen and lungs; tuberculosis of lungs and tracheobronchial lymph nodes; white male, aged 60, A-345.
5: Gastric carcinoma with metastases to regional lymph nodes, liver, lesser omentum and peritoneum; tuberculosis of lungs and tracheobronchial lymph nodes; black male, aged 40, A-1947.
6: Rectal carcinoma with metastases to pararectal tissues; generalized miliary tuberculosis; black female, aged 41, A-2037.
7: Rectal carcinoma with metastases to ovaries, liver and lymph nodes at hilum of liver; tuberculosis of lungs and spleen; black female, aged 71, A-2274.
8: Liver-cell carcinoma with metastases to lungs, pleurae, diaphragm and erosion into portal vein; tuberculosis of right lung; black male, aged 35, A-917.
9: Oesophageal carcinoma with metastases to liver; tuberculosis of right lung; white male, aged 58, A-3185.
10: Oesophageal carcinoma with metastases to lungs and tracheobronchial lymph nodes; bronchogenic carcinoma of right lung without metastases; tuberculosis of right lung; white female, aged 50, A-2913.
11: Bronchogenic carcinoma of left lung with metastases throughout lungs, tracheobronchial lymph nodes and brain[4]; tuberculosis of lungs; white male, aged 72, A-2512.
12: Tracheal carcinoma without metastases[5]; tuberculosis of lungs, tracheobronchial lymph nodes, spleen and liver; black female, aged 34, A-2717.
13: Breast carcinoma, right, with metastases to regional lymph nodes; tuberculosis of right lung; black female, aged 62, A-3108.
14: Uterine carcinoma, cervix, with metastases to retroperitoneal lymph nodes, left kidney, liver, spleen and lungs; tuberculosis of lungs; white female, aged 41, A-3251.
15: Uterine carcinoma, cervix, with metastases to regional lymph nodes, broad ligaments, peritoneum, omentum and mesentery; tuberculosis of lungs and spleen; black female, aged 40, A-463.
16: Pelvic carcinoma of undetermined origin involving ovaries, tubes and

[4] Previously reported: *Primary intrathoracic malignant tumors*, M. Pinson Neal, Southern M. J., 1933, *26*, 909.

[5] Previously reported: *Primary colloid adenocarcinoma of the lower third of the trachea*, W. Likely Simpson and Robert M. Moore, Ann. Otol., Rhin. & Laryngol., 1934, *43*, 1133.

pelvic bones, with metastases to peritoneum, sigmoid, caecum, ileum, mesenteric and retroperitoneal lymph nodes; tuberculosis of lungs, tracheobronchial lymph nodes and spleen; black female, aged 36, A-1952.

The remaining cases of combined tuberculosis and malignant tumor (other than of carcinomatous nature) were as follows:

17: Renal sarcoma with metastases to liver and inferior vena cava; tuberculosis of left lung; black female, aged 3, A-1245.
18: Hypernephroma without extension beyond the kidney; tuberculosis of liver; black male, aged 50, A-250.
19: Hypernephroma without extension beyond the kidney; tuberculosis of lungs and tracheobronchial lymph nodes; black male, aged 64, A-3114.
20: Hypernephroma without extension beyond the kidney; generalized miliary tuberculosis; black male, aged 30, A-419.
21: Pleural mesothelioma, right, with metastases to lungs, left pleura, tracheobronchial lymph nodes, liver, peritoneum and pericardium; tuberculosis of lungs and tracheobronchial lymph nodes; white male, aged 32, A-2552.

DISCUSSION

In a total of 105 cases of carcinoma (80.15 per cent of the total malignant tumors), the sixteen associated with tuberculosis comprise 76.19 per cent of the total malignant tumor-tuberculosis combinations.

Of the 105 cases of carcinoma, a total of 44 (41.90 per cent) were located in the alimentary canal as follows: oesophagus, 7; stomach, 23; small intestine, 2; caecum and colon, 5; and rectum, 7; and 9, or 20.45 per cent, of these were associated with tuberculosis. Of the 19 alimentary-canal carcinomata occurring in the white race, 6 (31.57 per cent) were associated with tuberculosis, while, of the 25 occurring in the black race, only 3 (12.00 per cent) were associated with tuberculosis.

Wilson and Maher have pointed out that "there does seem to be considerable evidence that cancer of the oesophagus is associated with pulmonary tuberculosis, as might perhaps be natural if the condition resulted in long-continued malnutrition." In the 7 cases of oesophageal carcinoma of this series, pulmonary tuberculosis was an associated lesion in 2 instances (28.57 per cent). Both cases occurred in the white race, while the 5 cases not associated with tuberculosis were found among the black males of 35 years of age and older. One of these (case 10, A-2913), a diffuse squamous-cell carcinoma of the oesophagus with extensive metastases to the lungs and tracheobronchial lymph nodes, associated with pulmonary tuberculosis, also showed the pres-

ence of a second malignant tumor. This was a bronchogenic carcinoma of miliary size, discovered quite by accident in the examination of the histological sections. Multiple primary tumors, when one is of microscopic size and obviously far from being capable of causing death, are of no unusual occurrence, according to Warren and Gates (4), who (5) have recently reported a case of multiple primary malignant tumors associated with tuberculosis.

The 5 cases of gastric carcinoma associated with tuberculosis constitute 21.73 per cent of the 23 cases of carcinoma of the stomach, but the surprising feature is that 4 (50.00 per cent) occurred in a total of 8 cases in white males 35 years of age and older, and only one (7.69 per cent) occurred in 13 cases of gastric carcinoma among the Negro males of the same age-group. In one of these (case 2, A-2517) the tuberculous and carcinomatous lesions were found in the same histological section from the stomach wall. Incidently, this is the only one of the 5 cases associated with tuberculosis that showed no metastases. No great significance can be attached to this as an antagonizing factor, since some of the gastric carcinomata not associated with tuberculosis in any form failed to metastasize before death.

In a total of 9 malignant tumors of the respiratory tract, irrespective of type, tuberculosis was found as an associated pulmonary lesion in 4 cases (44.44 per cent) as follows: mesothelioma of pleura, 2 cases, 1 with tuberculosis; bronchogenic carcinoma, 4 cases, 2 with tuberculosis; carcinoma of trachea, 1 case, with tuberculosis; and 1 case each of carcinoma of larynx and carcinoma of mucous membrane of the nasal sinus, each without any associated tuberculous lesion. Of these 9 cases, 3 occurred in the white race, and in all 3 (100 per cent) the respiratory-tract malignant tumor was associated with pulmonary tuberculosis; while, in the 6 cases occurring in the black race, only one (16.66 per cent) was associated with tuberculosis.

The single case of sarcoma and tuberculosis was the only one (9.09 per cent) encountered in a total of 11 sarcomata. The 3 cases of hypernephromata associated with tuberculosis constitute 42.85 per cent of the total 7 cases of hypernephroma. An unexplainable feature is that all of the hypernephromata occurred in the black race, as is the fact that none of the 3 cases associated with tuberculosis showed any extension beyond the kidney involved, while 2 of the remaining 4 cases not associated with tuberculosis showed extensive metastases to remote organs. In a total of 8 cases of malignant tumors of the kidney, ir-

respective of type, 4, or 50 per cent, showed evidence of an associated tuberculous lesion.

This study, concerning the incidence and relation of tuberculosis and malignant tumors in the same individual as seen at necropsy, has been presented notwithstanding knowledge of the diversity of opinion regarding the relative value of morbidity rates versus mortality rates and the reasons therefor. That this report is subject to criticism is undeniable, because (1) the relatively small number of cases on which calculations for the subgroups are dependent tends to inaccuracy; (2) the personal equation involved in the performance of the necropsies by several pathologists through a period of years; (3) the lack of a control group as employed in Pearl's study; and (4) the criteria for the classification of cases, particularly the tuberculous ones, are not universal. The fact that some statisticians are able to make their final conclusions coincide with preformed ideas concerning a subject has played no rôle in this report; it has been prepared and presented from an unbiased viewpoint.

CONCLUSION

In conclusion, it may safely be said that active tuberculosis and a malignant tumor are not infrequently found concomitantly in the same individual patient. This is particularly true of members of the white race, 35 years of age and older, when a malignant tumor of the oesophagus, stomach or respiratory tract is concerned. As yet, one cannot become dogmatic in any statement as to the exact relationship between these two conditions.

We wish to express our gratitude to Dr. M. Pinson Neal, Professor of Pathology, University of Missouri, Columbia, Missouri, for his aid and criticism in the preparation of this report.

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THE HOME VERSUS THE PREVENTORIUM IN THE MANAGEMENT OF TUBERCULOSIS CONTACTS[1]

LEWIS J. MOORMAN

The Oklahoma City Tuberculosis Dispensary was established in 1917. From the first, it has been its policy to consider the family the unit for dispensary work, with family and community education as the primary goal. Under this scheme, it has stressed the importance of case-finding, and attempted to examine all contacts, particularly those under sixteen years of age. In tables 1 to 3, we present the data revealed through the study of the Dispensary records on 1,322 children diagnosed and managed through the Dispensary during eighteen years.

TABLE 1

Tuberculin-sensitive and tuberculous children diagnosed and managed through the Oklahoma City Tuberculosis Dispensary, 1917 to 1935, inclusive

Total number	1,322
White	1,137
Colored	185
Age at time of admission	0–15 years
History of contact	
Known contact	1,058
No history of contact	132
Doubtful	132
Diagnosis at time of admission	
Childhood type	734
Definite parenchymal infiltration (pneumonic, miliary and adult type)	154
Tuberculous meningitis	1
Bone tuberculosis, including Pott's disease	5
Tuberculous cervical adenitis	3
Tuberculin sensitive without demonstrable pathological process	425

In view of the relatively large number diagnosed as having childhood type at first examination, attention should be called to the fact that many of these children were examined before the present criteria for X-ray interpretation were available. No doubt, shadows which would

[1] Presented at a session of the Clinical Section at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

now be attributed to blood-vessels were formerly regarded as calcified nodes. Attention is also called to the relatively high incidence of parenchymal infiltration. The majority of the studies with which these figures may be compared represent children of school age, while many of the cases included in this study were examined during infancy.

TABLE 2

Study of records with reference to deaths

Total number of deaths	28
Total number of deaths due to tuberculosis	18
Pulmonary tuberculosis	11
Tuberculous meningitis	4
Miliary tuberculosis	2
Tuberculosis of spine	1
Nontuberculous conditions	8
Possible tuberculosis	2

TABLE 3

Types eligible for admission to preventoria and number developing active tuberculosis

Total number eligible for admission	1,159
Number diagnosed as childhood type	734
Number found tuberculin sensitive without demonstrable pathological process	425
Number developing other types of tuberculosis while under observation (all colored)	4
Number of deaths in those developing other types (all colored)	4

A careful review of the records of the four cases mentioned, in table 3, as developing other types of tuberculosis, warrants the belief that three of them were developing acute generalized types at the time of first examination. If we eliminate these three cases, we then have 1,156 cases eligible (under existing criteria) for admission to preventoria, with only one of the 1,156 developing active pulmonary tuberculosis while under observation.

It is frankly admitted that our follow-up has been very imperfect, and no doubt deaths have occurred among those who have passed from our observation through change of residence, transfer to private physicians, etc. However, the average duration of observation and management is approximately two years, with an average of 400 children constantly under observation. Many cases have been under observation from four to six years and some have been followed as long as eighteen years. Given these considerations, it seems significant that, out of 1,156 cases, our records show only one death from tuberculosis, and that this one

case represents a colored child who had, in all probability, acquired massive infection through intimate contact in an unfavorable environment, before the time of first examination. While accurate figures for the total number of children covering the given period of time cannot be supplied, the evidence strongly supports the belief that, given a home program such as that supplied by the Oklahoma City Dispensary, the transition from tuberculin-sensitive and childhood type without active disease to the active progressive types with death is relatively uncommon.

These observations are in accord with the studies of Myers, Harrington, Stewart and Wulff (1), the results of which led them to recommend discontinuing the Lymanhurst School, devoted to the care of first-infection cases of tuberculosis.

A study of the literature dealing with the results of preventorium care is, with few exceptions, quite disappointing (2) (3) (4) (5) (6) (7), in that children returning from preventoria to their homes soon revert to former habits, discard or forget what they have learned, and often lose the weight gained in the preventorium. If we could have an up-to-date report on the cases handled by Hess (8) at Farmingdale in 1909 and during the years immediately following, we might have a better idea as to whether or not permanent favorable results follow preventorium management. When the Farmingdale Preventorium was handling 600 cases annually with an average stay of three months, Biggs (8) estimated that, in New York City alone, there were 40,000 cases in need of preventorium care.

Among the most interesting follow-up reports are those of Hawes and his associates. The first, published in 1929 (3), and covering 110 children discharged from Prendergast Preventorium from 1922 to 1926, carries a decided note of discouragement. Eleven of the cases returned for further treatment in the summer camp, and twenty for further preventorium treatment; seven of the group had developed pulmonary tuberculosis requiring sanatorium treatment. The average stay in the preventorium was seven months. The following is quoted from this report: "As I study the results of this investigation of 110 children discharged from our Preventorium during the years 1922 to 1926, I am more convinced than ever that the ultimate success of preventorium treatment depends upon thorough aggressive and prolonged follow-up work."

In June, 1934, Hawes, Wood and King (9) published *A Study of Ten Year's Work at the Prendergast Preventorium.* This report included 705 children: 404 had been permanent residents; and 301, members of the

summer camp. Of the 705 children during the ten-year period, only one died of tuberculosis and only two developed it in active or clinical form. In this report it was admitted that the good results were largely attributable to the careful follow-up of a highly trained nurse, serving as an after-care worker and securing the best possible home environment, plus adequate medical care. This followup was admittedly designed for the purpose of obtaining "coöperation of parents and other members of the family so that the training received at the preventorium is not dropped." The follow-up was so complete that only 29 of the total of 705 children could not be traced. The authors closed by suggesting the study of a similar group of children who have not had any preventorium experience and training.

At the 1935 meeting of the National Tuberculosis Association, Hawes reported such a study (10), with the following results: 705 children were studied and it was "found that 10 had since died of pulmonary tuberculosis as opposed to only one of the first group; and that 40 had come down with clinical pulmonary tuberculosis as compared with only three from the first group." The author closed with the following statement:

> If every summer camp and every preventorium will maintain this attitude and will insist that the six months' or year's stay at the preventorium or two or three months' stay at the summer camp means also that the nurse or follow-up worker goes into the child's home, takes active measures to remove the source of infection, sees that the other children are examined, instructs the parents in home hygiene and sees that after discharge these lessons are continued, no one, I am sure, will possibly doubt their educational value in our campaign against tuberculosis.

Considering the unfavorable comparison of the latter group, which Hawes designates as comparable with the preventorium group, it seems only fair to call attention to the fact that this group did not have the efficient follow-up and family supervision of a "highly trained nurse," but was wholly dependent upon the existing public-health program. From the standpoint of follow-up, home supervision and family education, the group here presented is more nearly comparable with the preventorium group, and, after allowing for sectional, environmental, and possibly racial, variations, it offers a more equable comparison for the study of relative results.

These most interesting reports on preventorium care are in accord with other less exhaustive follow-up studies, and clearly indicate that in

the last analysis desirable results are dependent upon a consideration of the family as a unit and a definite program within this unit; in other words, with family organization, family care and family education as the primary objects.

Attention is called to the fact that before the child arrives at an age commonly accepted as suitable for preventorium care, often the period of most intimate exposure has passed and the death quota from the acute forms of tuberculosis has been met (11), and that those surviving the hazards of the period of infancy have acquired the seeming immunity (12) which usually carries them safely on to the age of puberty, when many of them apparently suffer an equally inexplicable reduction in immunity (13). It is also pointed out that medical science provides no means of differentiating between the great majority who have acquired this immunity, and the unfortunate minority doomed to pass from the tuberculin-sensitive or inactive childhood type to active or manifest disease. Medical science is equally impotent in its efforts to discover those potentially in line for the great army who later develop adult types of manifest pulmonary tuberculosis. Consequently, the choice for preventorium care is without scientific guidance; therefore, we may be justified in saying that it should be all-inclusive.

It is evident that, even though the results warranted an all-inclusive preventorium program, the cost would be prohibitive. In view of this, together with the admission that in the preventorium plan the good results are dependent upon the family program, it would seem wise to consider seriously the comprehensive dispensary scheme, which, in addition to case-finding, family supervision, and family and community education, is definitely committed to the breaking of contact by removal of the patient from the home rather than removal of the exposed child. What has been said in this discussion does not apply to summer camps and preventorium schools. As a rule, summer camps, whether offering day care of twenty-four hours a day, are admitting children for a relatively short time. They are often maintained partially or wholly through voluntary donations with widespread community interest, and therefore possess a greater educational value than the preventorium maintained by the funds secured through taxation or organized voluntary agencies. The home life is interrupted for only a short time; consequently, the child does not lose his identity in the home program. Preventorium schools, open-air schools and open-window rooms in public schools do not interrupt home residence and should readily fit into and supplement the well-ordered home program.

Our present knowledge of the significance of sustained intimate contact and the behavior and course of tuberculosis in infancy and childhood, seems to warrant the action of Alfred F. Hess, when, in 1915 (11), he provided beds for infants under one year of age who were in contact with tuberculous mothers. Would it not be wise to make many of the now existing preventorium beds available for infants at a time when disease may be truly prevented and the mortality materially reduced?

It would also seem advisable to devote available beds to the more or less permanent residence for those children in homes where it is impossible to break contact or to improve environment, and to the temporary residence of those in homes where contact may be broken but where time is required to effect the removal of the patient from the home.

These suggestions are in line with our present concepts, in that active tuberculosis in infancy and childhood is primarily due to the reception of tubercle bacilli in massive dosage, or repeated moderate doses through daily contact resulting in cumulative massive dosage, and that the development and course of the disease are definitely, favorably or unfavorably influenced by environment. In order to favorably influence environment in a relatively permanent and effective manner, we must begin at home.

The child who helps to successfully work out the family program under existing financial and environmental handicaps will learn to appreciate the value of individual effort, the necessity of family responsibility, the need of community service, and the obligations of good citizenship. He will not only have an equal chance, with the preventorium child, to escape manifest tuberculosis, but he will be much better prepared to meet "manifest destiny."

Medical science, through knowledge of the causes and spread of tuberculosis, through modern diagnostic methods and scientific treatment, has provided adequate means of prevention. With tuberculin as our compass, the seas may be fairly well charted; the task now demands only intelligent application and execution. The control of tuberculosis clearly rests upon a comprehensive program which squarely faces the scientific facts of immunology and places in proper relation to society all the established principles of prevention and cure now available.

The family must be considered the unit (13) (14) (15) (16); the community the ultimate object of our attack. Treatment of tuberculosis must be individual; prevention must be wholesale. It is not enough to pour the healing oil and pay the keeper of the inn; we must "police the road to Jericho."

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THE DISSOCIATION OF TUBERCLE BACILLI[1]

WILLIAM H. OATWAY, JR. AND WILLIAM STEENKEN, JR.

Dissociation may be defined as the process, or the result, of separating two or more variants of a microörganism from a parent culture. The process has come to include such methods as will produce isolated colony-formation and will condition the growth of the component bacilli in a manner favoring their variation.

No theory as to the cause of dissociation is proved. It would seem that there are two processes which can produce the variants which arise from a culture: the one, a simple separation of bacilli which already possess distinct and different characteristics; and the other, the differentiation of bacilli which are multipotential into diverse types. The nature of the mechanics of the latter process must be speculative until more is known about bacterial inheritance and even the growth of the tubercle bacillus. Changes in the characteristics of the cell have been attributed, by analogy to other heredity methods, to an interruption in the integrity of cell-division. Such an effect could occur with, or because of, a variation in environment. It has been suggested that cytoplasmic, as well as nuclear, modification could result. There is increasing evidence that the characteristics of bacilli are inherited independently, though they are sometimes linked in typical ways.

The qualities of a culture of tubercle bacilli which may be affected by dissociation include colony morphology, chromogenicity, bacterial morphology, immunological properties, virulence, and chemical composition.

A mention of terminology might be appropriate at this point. The colony forms which have been described and photographed in the literature have several typical appearances and many intervening stages. The terms which have been applied to colonies on solid media describe gross shape, discreteness, erectness, peripheral spread, granularity, color, moistness, and greasiness; on fluid media, the position in relation to the surface, the gross shape, consistence, color of colonies, and color of the

[1] Presented at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

medium. The nomenclature of the variants has been obscure and confusing. The terms "R" and "S" were first used to mean *rough* and *smooth*; then to include resistance or sensitiveness to environment. Since certain strains of bacilli have yielded more than two variants, and since there is no invariable correlation between colony forms and certain levels of virulence in the avian, bovine and human bacillary types, it would seem best at present to denote variants by brief terms descriptive of strain source, colony morphology, and relative virulence. The colonies can be described in capital letters as "R" (rough) or "S" (smooth) with the modifying term "ch" to mean chromogenicity, and even a further descriptive letter to describe peculiar types of roughness. Subscriptions, in small letters, are added to denote virulence (v), avirulence (a), or an intermediate level (in). Thus, for instance, we have the H_{37} R_a, the avian Sch_a and the bovine S_a. This simplifies the problem to its fundamentals.

The variants of the several types of tubercle bacilli have several characteristic colony forms on solid plated media. The avian type has been found to have a rough crater, a smooth hemisphere, a pigmented smooth hemisphere, an unstable flat rough form, as well as a newly described stippled rough colony. The bovine type has generally been found to produce a smooth hemisphere and a rough colony. Strains of the human type have yielded a rough crater and a rough stippled form. A smooth hemisphere has also been found in cultures upon recovery from tissue lesions. In general, the smooth variants grow diffusely in a liquid medium and have, if any, a fine veil-like surface growth; rough variants grow on the surface as a coarse, curdy, lace-like pellicle.

Some workers have described colonies similar to the avian forms in both human and bovine strains. Certain strains of all three types have been found to contain the crater or worm-cast rough colony. The lack of further consistent similarities may be due to incomplete dissociation, technical or environmental differences, the time of observation, and the individual interpretation factor. To aid standardization of results the cultures should be "read" at the height of their active growth at four to six weeks, and only subcultures, not platings direct from lesions, should be considered typical.

Dissociation may proceed by two courses, namely, the "spontaneous" and the "forced." Spontaneous dissociation is an unplanned change which occurs in a strain of known quality; it may be sudden or gradual; it most often includes a degradation of virulence; and there are examples

of this change in every laboratory. Forced dissociation is an intentional procedure which includes a manipulation of the subculturing technique and a regulation of the environment.

There have been numerous methods suggested for "forcing" a dissociation. The bacilli can be assorted during subculture. A colony is selected because of its appearance; the bacilli are suspended in a liquid; and the suspension is diluted and filtered in such a way that, when it is planted on a plate of medium, single-colony growths will result. The isolation of single bacilli by a special technique has allowed a greater certainty concerning the origin of the resulting growth.

The environment must be controlled to produce an optimum for growth of a variant. The oxygen, carbon-dioxide, and vapor pressures can be regulated by the use of special banded plates or stoppered flasks. The medium should be of specific content and, except for the modification of one factor at a time, the same for all variants.

Bile salts were early suggested as an aid in producing degradation of a culture. They were considered to be most effective on bovine strains. Other workers have found virulent variants to grow well in bile-salt media; a false and transient greasy smoothness to be produced; and, when used on a suspension of bacilli, to occasionally cause a version to virulence.

The use of specially constituted media has been recommended as an aid to dissociation or version. Many of the results are no doubt coincidental and due to other factors; often they are contradictory. It would seem that changes in morphology, reproduction, and respiration caused by unusual nutrition should not be confused with bacterial variation.

Normal serum added to a medium has been found of some help in producing dissociation, but homologous variant anti-serum has been very successful. It supposedly inhibits the growth of the specific variant and has often been used to revert cultures of avirulent bacilli.

A most effective aid to dissociation has been the regulation of the acidity and alkalinity of the medium. It was first noted that a virulent human strain became degraded on acid veal broth. Then it was found that digestion of bacilli with acid favored a rough growth and with alkali a smooth one. It was also discovered, and recently further emphasized, that regulation of the pH level of the medium (all other factors being the same) favored a rapid and radical dissociation. A relatively acid pH is optimum for development of the avirulent variant; an alkaline

level maintains the virulent variant best. It has also been suggested that smaller differences of pH will produce other typical colonies, and that these levels and colonies are often correlated with virulence levels, and are similar in avian, bovine, and human strains.

Dissociation has been produced in human-type cultures by means of a lytic principle. This phenomenon developed on media which had become highly acid after an extended growth-period. The original virulent colonies were destroyed, and a new growth with a different colony form and a low virulence occurred. The original variant is definitely susceptible; the second is resistant and stable.

It has been reported that the addition of ferric chloride to a medium produces stable, virulent, smooth colonies of both avian and human strains.

The final method to be mentioned is the inoculation of guinea pigs with an undissociated culture and the recovery from the lymph-node abscesses of a more or less dissociated result. In general, this is considered to cause an increased number of virulent "S" colonies, but again contradictory results have been reported. The method has been modified by culturing the nodes at short intervals; by interval blood cultures; and by treatment of the animals after inoculation with an acetonic extract of tubercle bacilli.

There are several means of distinguishing between variants by testing the physical differences of the bacilli. The typical smooth variants are more easily emulsified or suspensible in normal saline solution than are the rough. Differences have been found in reaction of the media after growth of variants of mammalian and avian bacilli, but these reports are not consistent. When bacilli from recent or virulent smooth cultures are treated with acid solutions, agglutination occurs when relatively strong solutions are exhibited; avirulent or degraded rough cultures respond to less acid solutions. The avian levels are slightly higher than the mammalian for both variants. When the mobility velocity of bovine and avian variants was determined by cataphoresis, the R colonies were found to have a lower velocity than the S.

The application of dissociation methods has resulted in the recognition of variants, or the dominant variant, from every conceivable source. All pathogenic and many nonpathogenic acid-fast types, many famous laboratory strains, pathological tissues and fluids, pus, blood, and sputum have all yielded results. Avian is said to be the easiest type to dissociate; assortment alone may be sufficient and, although it is less

sensitive to pH changes than other types, such a regulation helps; bovine is the next easiest; and human is most difficult. The R1 strain has not been successfully reverted; *BCG* is considered to have become increasingly difficult to dissociate or revert after further years of subculture. Both of these, and other similar strains, are now probably almost pure-line R_a cultures.

The direction of most changes *in vitro* has been toward lessened virulence. This has been the most natural trend, it has been produced most easily, and the variation has been widest. The dissociation of virulent cultures has been much less difficult than the reverse.

A constant relationship between colony morphology and virulence has not been invariably found. It has been suggested that strains of high virulence produce many smooth colonies and that avirulent colonies are quite often rough; that the major pathogenic property may be associated with one form; but dissociation of colony form may occur irrespective of virulence.

Chemical analysis of completely dissociated variants obtained under standardized conditions has seldom been made, unfortunately. The quantitative accuracy of the analyses and the purity of the fractions are improved, but separation without denaturization is not yet accomplished. Differences which have been found between variants, chiefly in the lipin content, were correlated with the variant and type of bacillus used, the type of medium, and its pH at the start of growth.

The difference in composition of the dissociates is an extremely important point, since each of the qualities of the bacillus which have been named (colony form, chromogenicity, bacterial morphology, and the immunological properties) are apparently related to the composition; even virulence may prove to be a function of chemistry. Since environment modifies growth and composition, it is obvious how important a regulation of this factor must be.

Chromogenicity is a property of certain variants. When the pigmentation is present under regulated cultural conditions it can be considered a quality of the variant. It has been found to vary with the composition of the medium, the temperature of the environment, the age of the culture. Certain of the acid-fast bacilli have been found to synthesize carotene, the quantities of which are correlated with intensity of color. However, carotenoids are found only in nonpathogenic acid-fast strains. A pigment substance has been isolated from a human strain, identified, named "phthiocol," its reactions and properties observed, and an identical substance synthesized.

The immunological properties of dissociated variants have been considerably studied and with more coherence of results than usual. The so-called "S" has usually been associated with immunological specificity. It is the more antigenic. ("S" in this case is found to mean virulence, not smoothness *per se*, and includes the R_v and S_v variants.) Degraded cultures, cultures which are mostly R_a, have a poor efficiency in producing immunity. We have found the avian R_a crater colony to be weakly antigenic. Vaccines composed of killed "S" bacilli have been found to give better protection than either living virulent or avirulent cultures. We have found, in testing tuberculous cases with O. T. preparations of the H_{37} culture and its two dissociates, that the R_v (or "S") variant evokes reactions at greater dilutions than either of the others. There is some evidence that there is also a qualitative difference. The composition of these tuberculins must be checked by purified protein extractions to determine whether there are quantitative or qualitative differences.

It is said that both "S" and "R" contain group-specific antigens, but that "S" contains a variant-specific antigen. When used in tests against sera of infected patients or animals, "S" antigen has been variously claimed to be specific for the diagnosis of disease; equal in effect with "R" in chronic disease; nonspecific for the grade of disease; or able to fix twice as much complement as "R"—producing an elevated S/R ratio—in acute tuberculosis. The opsonification of tuberculous serum is greater for "S" than for "R" bacilli.

Morphology and staining characteristics of the variants can be related only indefinitely at present to their other qualities. Reports concerning fixed preparations of the organisms suggest that their tinctorial reactions vary irregularly according to the cultural environment, the duration of growth, position in the colony, and the type of bacillus. In certain studies on avian and human strains the variants of low virulence tended to be the most pleomorphic and the least acid-fast, especially during their early stages of growth.

Microscopic and micromotion pictures of single-cell and microcolony preparations have shown differences in growth of the "R" and "S." The "R" bacilli of avian and cold-blooded strains grew closely in a dense net; the "S" forms grew loosely and a viscous intercellular material was noted. There has been scant help in such studies for the life-cycle theories; division was found to be by binary fission, and the length of the bacilli to depend on the ratio between the rate of division to the rate of growth. "R" and "S" forms have also been described as the

stable, acid-fast, vegetative stages in a growth-cycle of seven stages. Perhaps the changing morphology during growth is dependent on type of variant and the environment.

The virulence of variants has not always been affected in the dissociations reported. When the change occurs and if the dissociation has been complete, the difference may be definite and radical. We have regularly dissociated virulent cultures by forcing methods or the use of metabolic products, and have recently obtained variants from two well-known human and avian strains. The differences in virulence were considerable and quite stable except for a slight refinement of the quality after repeated subculture under optimal conditions.

Virulence of the variant was found to be the chief factor in the control of its pathogenicity. When the other factors known to modify the results of infection, such as the size of the infecting dose, the route, duration and site of infection, the species and individual resistance, the ages of host and culture, and the virulence of the organism, were considered, virulence was most important in its effects on the host-parasite relationship. A strain of bacilli, dissociated *in vitro* into two variants, allows the host two widely varying means of response—a domination or a susceptibility. The responsibility is increasingly bacillary.

The progress of infection was found to depend on the same formula which applies to undissociated cultures,—Resistance of the Host equals (=) the Virulence times (×) the Number of Bacilli. The relative virulence was directly correlated with the speed and intensity of the initial reaction, the type of disease as shown by fixed- and supravital-tissue studies and the leucocyte reaction, the amount of gross and microscopic disease, the number of bacilli in smears and lesions, and the mortality figures. The virulent variants caused large, rapidly growing, spreading lesions with evidences of acute inflammation, allergy and necrosis, many tubercle bacilli, maturation of the monocytes, and many neutrophiles. The virulent avian variant was lethal for rabbits and chickens; the virulent human was lethal for guinea pigs and occasionally for rabbits. The avirulent variant produced small, slowly growing lesions which regressed early, showed slight or no evidence of allergy or acute inflammation, contained very few bacilli, and the monocytes were only slightly matured. The avirulent avian and human variants were almost nonpathogenic in all species in the doses used. The intermediate variants produced an intermediate type of disease.

One can believe that the reaction to tubercle bacilli is due to their

particulate nature, their chemical composition, and their power of propagation in an environment. There would seem to be a single course of tubercle development, with the small, sluggish, regressive tubercle at the lowest form (similar to that produced by killed bacilli, etc.) and the rapidly progressive large tubercle with necrosis as its highest form. Virulence of the bacillus is the chief factor which dictates how far in this course the tubercle shall progress. Other factors are effective but overshadowed. We have only meagre evidence that differing bacillary composition produces specific pathogenic effects; such differences are logical but must be determined with nonreproducing (dead) bacilli.

Dissociation of intact cultures has been discussed. A similar step is version of the colonies of one variant, with a specific form and degree of virulence, into another variant. This course has been accomplished many times with different strains of bacilli. Version can occur when the pH level of the medium is changed from that of the variant in use to the optimum for its converse. Avian and human "S" variants have been changed to "R", and "R" to "S", in this manner. Inoculation of a variant into animals has been used to produce both types of colonies, but is most valuable in obtaining virulent from avirulent variants. It is said that late in the disease, after the inoculation of an intact strain into a susceptible animal, one may obtain a predominance of virulent "S" colonies, and from a resistant animal, at an early date while bacilli are present, many avirulent "R" forms. Other methods have also been described. The use of the isolation and growth of single bacilli should tend to assure us that the version changes are in the individual organisms, and not due to a mixture. A European writer has recently called certain cultures mixtures which include saprophytes. This is a matter to be guarded against, but there is sufficient evidence against contamination in general. We have repeated the dissociation of the H37 human strain five times into similar virulent and avirulent variants of distinctive morphology; produced "R" to "S" and "S" to "R" version; obtained constant results from virulence tests, with the same ratio between virulent and avirulent variants in rabbits and guinea pigs, and with each variant being relatively more virulent for the guinea pig than the rabbit. We have never found an avian or human variant to have the peculiar growth characteristics of a saprophyte. A French group believes "S" to be the low-grade variant, with "S" forms dominant in avian cultures, intermediate forms in bovine cultures, and "R" forms in human cultures. They believe that this is evidence that all

bacilli are derived from a low-grade primary "S" strain and arrive at "R" and virulence slowly by animal passage.

There are numerous clinical implications of dissociation. The knowledge that degradation often involves the loss of valuable antigenic properties may modify the use of certain living vaccines (such as *BCG*), and determine the type of killed organisms to be used. It is possible that aid in the diagnosis of activity in pulmonary disease can be had from the appearance of sputum cultures. It may be worthwhile to attempt application *in vivo* of methods used to produce an unfavorable environment for virulent bacilli *in vitro*.

The aims of experimental work now in progress are to determine more certainly the antigenic and vaccinating values of the variants, to determine the nature and application of the lytic principle, to discover the relationship of dissociation to the life and growth of cultures, and to determine and elaborate the fundamentals and methods of dissociation.

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THE DISSOCIATION OF AN OLD HOMOGENIZED CULTURE OF THE HUMAN TUBERCLE BACILLUS[1]

RANDLE C. ROSENBERGER

This particular growth of the human tubercle bacillus has been under constant cultivation upon glycerin-agar since 1903. It is from homogenized bouillon growth and, until seven or eight years ago, grew or developed upon glycerin-agar as a soft, creamy growth, granular in appearance, or, to use the modern term, *rough* (R).

It was never characterized on glycerin-agar by isolated, dry, adherent colonies, as tubercle bacilli of human or bovine source generally develop, but extended readily and evenly over the entire surface of the slant.

The organism was primarily isolated from a mesenteric lymph node upon glycerin-potato and then homogenized in glycerin-bouillon. From the bouillon it was transferred to glycerin-agar, and from time to time, for demonstration purposes, it was reinoculated into glycerin-bouillon and again homogenized by shaking intermittently, thus allowing no sediment or pellicle to form. If shaking was not resorted to, it would quickly form a pellicle, together with a sediment in the bouillon.

The reaction of the glycerin-agar and glycerin-bouillon was tested originally with litmus paper or phenolphthalin until the pH method was brought forward in 1920. Since this time the reaction of the medium has been tested by the pH technique.

The culture (on glycerin-agar) was kept under observation at 37°C., and reinoculations made every six weeks, though sometimes not until eight or twelve weeks. Growth was always comparatively rapid and abundant. The organisms making up the growth were "typical" in their morphology and staining reactions, but, if allowed to develop for several months in bouillon, clubbed, branched, filamentous, and granular or "beaded" forms could be observed. Such types I reported in *American Medicine*, April 22, 1905.

Having grown the organism for a number of years and observing nothing very unusual in its behavior, I was surprised to find upon one

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occasion (eight years ago) that instead of the generally rough characteristic, the whole growth was of a smooth glistening, honey-like appearance. This growth was not tenacious or slimy in consistency; a small mass could easily be removed by platinum wire, without any stringy characteristic. Smears were made, and the organisms were generally acid-fast, and some short filamentous forms were present, although the greater number resembled "ordinary" tubercle bacilli. At first thought, I believed that a contamination had taken place, but the spread showing only acid-fast organisms led me to believe that dissociation had taken place and the R had changed to the S type.

Inoculated into glycerin-bouillon a pellicle formed upon its surface, and from this pellicle, inoculations were made upon glycerin-agar. A growth resulted, which again was smooth and made its appearance within three to four days. This procedure was repeated a number of times,—inoculation from glycerin-agar into glycerin-bouillon, and from glycerin-bouillon into glycerin-agar,—and the results were invariably the same for a number of months.

Instead of discarding these growths, they were kept for longer intervals, and, at the end of from ten days to three weeks, at the periphery of the S growth could be observed small masses, outcroppings or islands, that bore the appearances of the original R strain. By fishing out these small R masses and implanting them upon plates and tubes of glycerin-agar, eventually a general R growth was obtained. From the preparation, reinoculations gave a similar (S) growth, but every now and then in the culture were observed the R masses springing from some point of the S growth.

Throughout this time (eight years) stained spreads showed most unusual morphological forms. There were observed distinctly coccoid elements in the early days of growth, some of which were acid-fast, and others not acid-fast. There were rods with a terminal or eccentrically placed somatic granule, the latter staining very deeply with the fuchsin, while the body of the organism stained very faintly with the counterstain. In one or two preparations minute oval (some spherical) transparent bodies, resembling free spores, were present. Only two or three of these bodies were seen in some spreads, but in others there were many. When the organism took on "typical" bacillary elements, then these spherical bodies disappeared. In some cultures, short acid-fast filaments were seen with deeply staining granule at both ends of the filament.

After the culture had grown for several weeks, the following forms were observed: short, straight, bacilli, staining solidly; others, granular

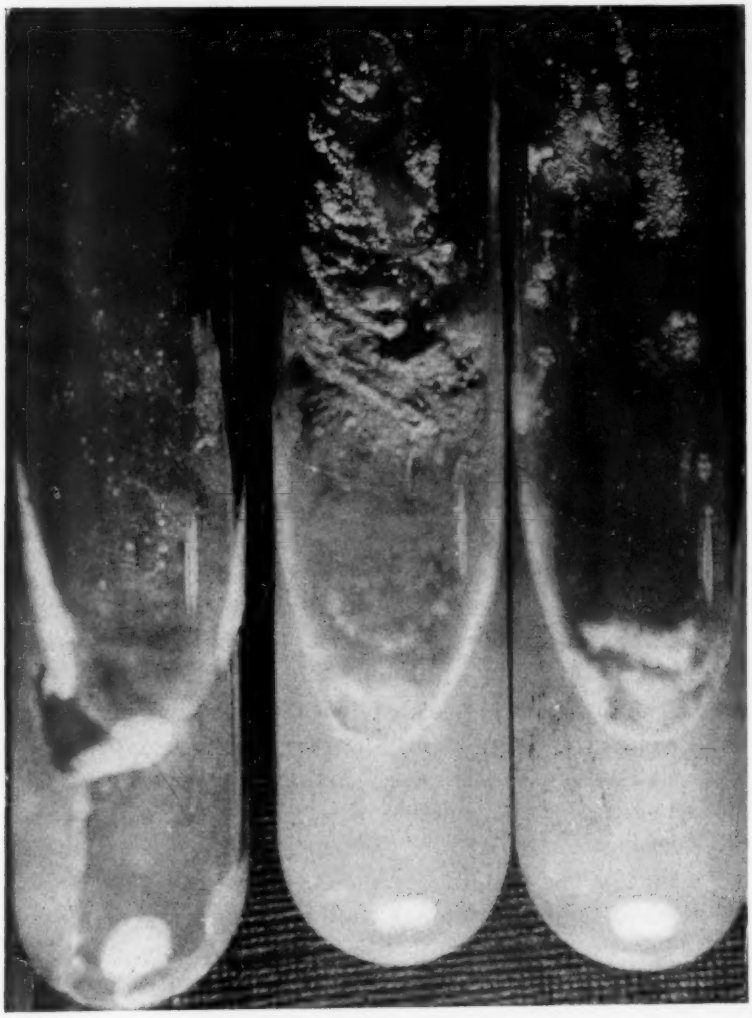

Fig. 1. Three tubes showing the growth of the homogenized human tubercle bacillus on glycerin-agar. The S (smooth) growth extends over the whole surface of the slant with outcroppings here and there of R (rough) strain.

or "beaded," and a great many minute coccoid forms; all were acid-fast. Regarding the acid-fastness, some were more intensely stained

than others, that is, a bright red, while a great many were dull red and some pinkish. The spreads were stained with carbol-fuchsin, and were then decolorized with 3 per cent hydrochloric acid in alcohol or 3 per cent hydrochloric acid in water. Pappenheim's reagent was also used as a decolorizing agent and counter-stain.

During all this time I persisted in the use of glycerin-agar and glycerin-bouillon for cultivation. Believing that the reaction of the culture medium had something to do with the bacterial variation, inoculations were made upon glycerin-agar with reactions of pH 7, 7.2 and 7.4, as well as the usual medium with reaction of pH 7.6. Upon all of these media of different reactions, the results of the inoculations were the same; that is, some would give a smooth glistening growth while other inoculations gave a rough surface. In either one, after a week or two, R growths would make their appearance on the S, and S growths would appear upon the R tubes.

At first glance at the glistening S growth, one would think immediately of a contamination having occurred in the culture; it resembled the honey-like growth of *B. mallei*. Again, in some of these a growth would appear within 48 to 72 hours; and, in each instance where spreads were made and stained by an acid-fast technique, most of the organisms were non-acid-fast. Spreads made after ten days or two weeks from the identical culture showed the great majority of organisms to be acid-fast.

It was by persistently repeated inoculations from glycerin-agar to glycerin-bouillon, and *vice versa*, for months and months, that I was able to isolate an apparently pure R and an S type of organism. Having no apparatus for the isolation of single organisms, it was just this repeated fishing that eventually gave an R and S type separately.

Later, inoculations were made upon Loewenstein's medium, Corper's potato medium and glycerin-agar: all resulting growths were of the S type. Three months later, inoculations were made from these upon glycerin-agar, pH 7.6, and up to the present time (1936) the growth is of the R (rough) type, creamy in consistence and easily homogenized in bouillon. Upon a number of occasions, I inoculated rabbits and guinea pigs intraperitoneally, with both the S and R types, but no lesions were demonstrable after six to eight weeks. Inoculations into the massaged groin of a guinea pig failed to produce lesions with either strain.

One rabbit was inoculated with 5 cc. of a homogenized bouillon culture of the R type intravenously, but no lesions developed.

SUMMARY

This is the history of a human tubercle bacillus which was obtained from a mesenteric lymph node in 1903.

It was homogenized, and has been grown since the date of its isolation, being inoculated from glycerin-agar to glycerin-agar from time to time.

About eight years ago it suddenly took on unusual characteristics, appearing as a uniformly S or smooth form.

By persistent inoculation and reinoculation from glycerin-agar to bouillon at irregular periods of time, and from glycerin-bouillon to glycerin-agar, two forms were eventually grown, R and S.

This dissociation persisted for eight years, but, finally, there was a return to the original soft, creamy, granular or R growth.

THE DESTRUCTION OF CERTAIN CONSTITUENTS OF THE TUBERCLE BACILLUS BY BACTERIAL ENZYMES[1]

FREDERICK J. WALLACE AND H. A. BRAY[2]

The studies of Levene (1), Tamura (2), Heidelberger and Menzel (3), Anderson (4), and others have demonstrated the presence of carbohydrates in the tubercle bacillus. The relationship of carbohydrates to virulence was established for the pneumococcus type III by Avery and his associates (5). These investigators also discovered that virulent forms of type III pneumococci can be rendered avirulent by removal of the carbohydrates in the capsule of the pneumococci by bacterial fermentation. The above observations, together with the knowledge that certain bacteria are capable of decomposing carbohydrates identical to some of those present in the tubercle bacillus, prompted us to investigate the possibility of modifying the carbohydrates of the tubercle bacillus by bacterial action. We selected for this purpose, *Lactobacillus pentoaceticus* and the *Bacillus macerans*.

L. pentoaceticus, originally isolated from sauerkraut, corn silage and manure, possesses the ability to convert pentose sugars, such as arabinose and xylose, into lactic and acetic acids. It can also convert hexose sugars, such as dextrose and galactose, into lactic and acetic acids. *B. macerans*, originally isolated from vats of retting flax, can decompose waxy substances, polysaccharides such as starch and pectin, and monosaccharides such as arabinose, mannose and galactose.

EXPERIMENTAL DETERMINATION OF TOTAL CARBOHYDRATES OF THE TUBERCLE BACILLUS

Most of the carbohydrates of the tubercle bacillus exist as free polysaccharides or monosaccharides (arabinose, galactose and mannose) strongly linked to other organic molecules. Acid hydrolysis is necessary to break up the organic combinations and liberate the carbohydrates so that they can be measured as reducing sugars. The optimum condi-

[1] Presented at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

[2] New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

tions for hydrolysis of tubercle bacilli were determined by hydrolyzing one-gram portions of moist bacilli (75 per cent H_2O) with various amounts of normal sulphuric acid, under a reflux condenser on an electric hot plate, for periods of from one to thirty-six hours. After hydrolysis, the sulphuric acid was removed quantitatively with barium hydroxide; proteins were removed by precipitation with lead acetate; excess lead was removed by precipitation with potassium oxalate; and reducing sugars were determined by the Munson Walker method. The maximum yield of carbohydrates from tubercle bacilli (strain H37), cultivated on Long's synthetic medium, was obtained by hydrolysis with an amount of NH_2SO_4 equal to 75 times the dry weight of the bacilli. The maximum period for hydrolysis was not constant, but varied from 6 to 21 hours with different cultures of tubercle bacilli (strain H37).

TABLE 1*

Carbohydrate content of tubercle bacilli (strain H37)

TIME OF HYDROLYSIS	H37 ON LONG'S MEDIUM	H37 ON LONG'S MEDIUM	H37 ON LONG'S MEDIUM	H37 ON GLYCEROL-BROTH
hours	*per cent*	*per cent*	*per cent*	*per cent*
6	11.9	11.0	1.5	23.5
9	10.4	11.1	6.3	24.2
12	6.0	11.5	10.0	23.0
15	8.6	12.1	9.4	25.1
18	8.4	13.4	9.5	23.7
21	8.2	14.4	9.9	20.4
24	7.2	12.3	6.9	14.3
36	2.2	11.7	6.3	0.0

The amount of carbohydrate recovered was much greater when the tubercle bacilli were grown on glycerol-broth. The carbohydrates were calculated to dextrose on the basis of the dry weight of the bacilli. Representative analyses are presented in table 1.

DESTRUCTION OF THE CARBOHYDRATES OF THE TUBERCLE BACILLUS BY LACTOBACILLUS PENTOACETICUS

The carbohydrates of the tubercle bacillus, whether in the form of the hydrolysate, or present in dead or in living virulent bacilli, are destroyed by *L. pentoaceticus.*

The hydrolysate: This was obtained by the following chemical procedures: Large quantities of tubercle bacilli (strain H37), cultivated on Long's synthetic medium, were filtered on a Buchner funnel, washed

with distilled water, and hydrolyzed under optimum conditions. After hydrolysis the sulphuric acid was removed quantitatively with barium hydroxide. Protein-free portions of the solution gave reducing sugar values of 0.145 per cent, as calculated to dextrose on the weight of the solution. Nitrogen and phosphorus determinations indicated the presence of these elements in sufficient amounts to support bacterial growth. The hydrogen-ion concentration of the hydrolysate was adjusted to pH7: and 200-cc. portions of the hydrolysate were then dispensed in flasks, and sufficient calcium carbonate was added to neutralize any acidity which might develop. The flasks were autoclaved for twenty minutes at 15-pounds pressure, cooled, and inoculated with a culture of *L. pentoaceticus*, taken from casein-gelatin-agar medium. Microscopic examination revealed profuse bacterial growth at 24 hours. Analyses for carbohydrate were made at intervals of 24, 48 and 72 hours. At the end of 72 hours, analyses showed a complete destruction of sugar.

Dead tubercle bacilli: The following procedure was adopted to acclimate the *L. pentoaceticus* to dead tubercle bacilli: A series of flasks was prepared, containing decreasing amounts of hydrolysate and increasing amounts of dead tubercle bacilli, sterile water and sufficient quantities of calcium carbonate to neutralize any acidity which might develop. The flasks were inoculated progressively, each from the preceding flask, until growth was sustained in the last flask containing dead tubercle bacilli, calcium carbonate and water.

Carbohydrate determinations of the dead tubercle bacilli showed at the beginning of the experiment 9.5 per cent of carbohydrate. The carbohydrates were reduced to 4.6 per cent at the end of the tenth day. They had disappeared by the 25th day.

Living virulent tubercle bacilli: A series of flasks was prepared, containing 200 cc. of dextrose-peptone-broth and suitable amounts of calcium carbonate. The flasks were inoculated with a culture of *L. pentoaceticus*. The dextrose in the culture was completely decomposed at the end of 72 hours. At this time a suspension containing one gram of moist tubercle bacilli (strain H37), cultivated on Long's synthetic medium, filtered on a Buchner funnel, and washed with sterile distilled water, was added to each flask. The flasks, forty-seven in number, were incubated at 37.5°C., for 30 days, and the contents were then hydrolyzed.

The experiment was controlled by incubating for a similar period

a series of 18 flasks containing 1 gram of living tubercle bacilli in 200 cc. of distilled water. The maximum reduction of carbohydrate in the controls was approximately 12 per cent. The reduction of carbohydrates in four flasks containing tubercle bacilli and *L. pentoaceticus* was 97 per cent. In the remaining 43 flasks, the carbohydrates were completely destroyed.

DESTRUCTION OF THE CARBOHYDRATES OF THE TUBERCLE BACILLUS BY BACILLUS MACERANS

Experiments conducted along the same lines as for the *L. pentoaceticus* were made with the *B. macerans*. Complete destruction of the carbohydrates of living tubercle bacilli occurred in a series of experiments totalling 52 flasks. In two series of experiments, the carbohydrates were completely destroyed in eight days.

In other words, chemical tests have been repeated sufficiently often to warrant the conclusion that the carbohydrates of the tubercle bacillus can be completely destroyed by bacterial ferments.

MICROSCOPIC EXAMINATIONS

Microscopic examination of the contents of the control flasks at the end of twenty-eight days (tubercle bacilli implanted in peptone-broth, dextrose-peptone-broth and distilled water) showed no reduction in the number of tubercle bacilli, although a few were vacuolated and beaded. However, microscopic examination of tubercle bacilli implanted in cultures of *L. pentoaceticus* showed striking changes. During the first week, the tubercle bacilli were surrounded by masses of *L. pentoaceticus*. After this time there was a gradual diminution in the number of tubercle bacilli. At the end of four weeks the number of acid-fast rods was markedly reduced. In some instances there were only one or two acid-fast rods per oil-immersion field.

Similar results were obtained with the *B. macerans*. Occasionally microscopic examination failed to show any acid-fast bacilli.

Instances occurred both with *L. pentoaceticus* and with *B. macerans* when a fair number of tubercle bacilli were observed at the end of thirty days. In such instances, the *L. pentoaceticus* were few in number and the *B. macerans* were in a sporulating state. The striking reduction in the number of tubercle bacilli, when incubated with the *L. pentoaceticus* and with the *B. macerans*, suggest that these microörganisms destroy not only the carbohydrate fraction of the tubercle bacilli but

other components. This view is supported by chemical analyses which indicate that partial protein degradation results from the action of *L. pentoaceticus* on the tubercle bacilli.

SUMMARY

1. The carbohydrate content of tubercle bacilli (strain H37), cultivated on Long's synthetic medium, is not constant. The maximum yield in different cultures varied from 10 to 14.4 per cent.

2. The free and combined carbohydrates of virulent tubercle bacilli (strain H37) are destroyed by *L. pentoaceticus* and *B. macerans*.

The authors wish to express their appreciation for the help of Mr. Joseph M. Kurung, to whom they are greatly indebted for technical assistance.

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ON THE BIOLOGICAL ANTAGONISM BETWEEN SMEGMA BACILLI AND TUBERCLE BACILLI[1,2]

HENRY SEWALL AND EUGENE C. DE SAVITSCH

HISTORY OF THE SMEGMA BACILLUS

In 1884, Sigmund Lustgarten reported finding in sections of syphilitic tissues, treated by a special method of stain, a peculiar bacillus which he believed to be the specific cause of syphilis (13). This opinion was endorsed by no less an authority than Carl Weigert (in whose laboratory the work (22) seems to have been done), and in 1885 Babes is reported to have reached the same conclusion.

Within a year, Alvarez and Tavel (2), from the laboratory of Cornil at Paris, reported finding in the epithelial secretions from the genital mucous membrane of healthy people bacilli which, in their morphology and tinctorial reactions, agreed in all respects with the Lustgarten bacteria of syphilis. Probably because the French investigators found the bacilli in the preputial smegma of healthy males and in secretions between the labia in the female, the germs at once received their name of *Smegma bacilli*. But their normal habitat is probably coextensive with the epithelial covering of the body, organisms answering their description having been found in ear-wax, secretions of the umbilical sulcus and the scurf between the toes.

Until the discovery of the *Treponema pallidum* in 1905, a prime stimulus to investigation of the smegma bacillus perhaps lay in its alleged identity with the bacillus of Lustgarten. Especially in the late '80s we find this question of aetiology engaging medical conferences and current literature. The smegma bacillus discovered by Alvarez and Tavel soon attracted intensive investigation on its own account. Bitter found considerable variation in the form, size and staining qualities of the microorganisms, which he presumed to classify under eight distinct groups (4). While the Lustgarten bacillus occurred but sparsely and always within tissue cells, the smegma germs were found free and often in great numbers.

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] Assisted by a grant from the Henry Strong Denison Foundation for Medical Research.

The so-called smegma organism was easily secured for examination and was generally admitted to closely resemble in form, size and acid-fastness the bacilli of tuberculosis and of leprosy. Though easy to demonstrate in either the normal or diseased body, smegma bacilli long resisted all attempts at artificial cultivation.

Laser (11), and also Czaplewski (7), accidently encountered acid-fast bacilli in venereal secretions which they claimed to have grown in pure culture. The former succeeded in securing growth on blood-covered agar.

Novy adds the suspected material to melted agar, which has been cooled to 50°C. and, after receiving a small amount of human blood, is deposited in a Petri dish and incubated at 37°C. After a day or two, the colonies should be examined for bacilli, which, after staining, resist decoloration by acids (17).

The most satisfactory account we have found of methods for obtaining smegma bacilli in pure culture is that of Alfred Moeller (14). This author refers to a common experience of workers who reported a great diminution in the degree of acid-fastness in the germs of smegma after repeated cultivations (15). Neufeld had become convinced that in smegma there occur at least two different indistinguishable acid-fast bacilli. One, a diphtheroid form, could be reproduced in pure culture but lost its ability to resist acid; the other, of tuberculoid character, the *true* smegma bacillus, continued acid-fast but could not be grown in pure culture.

It is this tuberculoid form, or true smegma bacillus, that Moeller, taking advantage of an accidental observation, claims to have obtained in pure culture. He had found the detritus of serum, formed in healthy skin with fly-blisters, to contain acid-fast bacilli. When the fluid was withdrawn and incubated, after three or four days there was enormous increase of the germs, and transfer could be made to artificial media. He also grew the bacilli from the secretion within the navel when planted in human serum. He describes this bacillus as absolutely acid-fast and alcohol-fast, whatever the nature of the culture medium on which it is grown, its differential staining being just like that of the tubercle bacillus. After 25 generations of artificial cultivation the acid- and alcohol-fastness remained as in the original culture.

The germs manifested great greed for oxygen; they grew upon all ordinary media; the first colonies developed slowly, in about three days; in later generations colonies may appear in twenty-four hours.

Moeller's article (14) is the most definite and satisfactory contribution to the subject we have seen; nevertheless, we manifestly are but at the beginning of knowledge of the great group of acid-fast organisms in general, not to mention their individual functional specificities. Moeller, himself (15), had made a noteworthy attempt to differentiate various members of the group by their properties. He found that the acid-fast bacilli cultivated from hay or manure would occasionally, when inoculated in pure cultures into guinea pigs, produce tubercles and even cavity-formation. He says, "The post-mortem appearance is usually different from that of tuberculosis, but in many cases the picture is confusingly similar." He suggests that these forms may even be transformed into tubercle bacilli. Somewhat similar statements have been made regarding smegma bacilli.

Krause and Baldwin, fifteen years later, attacked this same problem armed with all our modern conceptions of immune processes, and may be said to have serviceably defined the profound complexity of the subject (10).

Abbott and Gildersleeve had already discussed the "etiological significance of the acid-resisting group of bacteria and the evidence in favor of their botanical relation to bacillus tuberculosis" (1). They conclude that "the designation of bacillus as applied to this group of bacteria and to the exciter of tuberculosis is a misnomer; they are more correctly classified as 'actinomycoses'."

Barannikow (3) early attempted to define the characters of the smegma bacillus; and the papers of Dahms (8) and of Brereton and Smith (6), respectively, furnish good bibliographies and useful information.

Recent researches have been directed chiefly toward the determination of functional relationships between various members of the acid-fast group of bacilli and to the cellular reactions evoked by them.

Furth (9) made important studies on the differentiation of various varieties of acid-fast bacilli on a serological basis. He writes: "There are qualitative differences in the antigenic structures of various acid-fast bacilli. Mammalian tubercle bacilli have an antigenic structure different from all other acid-fast bacilli. Acid-fast saprophytes differ qualitatively from all other acid-fast bacteria." But, within this group, "There is at least one fixed sub-type, for strains from various sources such as those designated as 'smegma,' 'mist,' 'milk,' 'pseudo-tuberculosis,' and 'butter R.,' have been found to be closely related if not identical."

Sabin (18) declares, "The monocyte cell bears a specific relationship to tuberculosis, not only because it is the forerunner of the cell which is the structural unit of the tubercle, but also because it is probable that the tubercle bacillus is able to survive for long periods of time within this cell."

Schwartz and Cunningham (19) inoculated rabbits by the vein with pure cultures of smegma bacilli and studied the effect upon the blood and tissues,

> to determine whether these reactions had any common factors with those seen after inoculation with virulent tubercle bacilli. The results are categorically definite showing that there is at least one clear-cut similarity in the two types of infection, that is, the increase in the number of monocytes of the circulating blood and tissues and the modification of these in the direction of the so-called epithelioid cells. That the smegma bacillus is not especially toxic is amply indicated by the long course pursued by some of these animals without any change in the blood counts; but when sufficiently large numbers of the micro-organisms were injected the animals developed massive lesions of the lungs and other tissues and finally died from the effect of the lesions.

They conclude that the similarity of reaction in the two forms of bacilli indicates that some common property, as yet unknown, exists in the two microörganisms; and add, "It seems probable that this property is not present to such a large extent in leprosy bacilli." It is probable that the doses of smegma bacilli used by these authors commonly far exceeded any used by us and, as stated, they used rabbits, not guinea pigs.

Suggestive observations on little studied chemicophysical reactions are presented by Stuart and Emily Mudd (16). These investigators found that acid-fast bacteria, studied by the interfacial tension method, contrast in behavior with all other cells: "that these surfaces are profoundly modified as result of interaction with serum; and that the acid-fast staining property is independent of the state of the surface."

As part of a general investigation of acid-fast bacilli, Long and Vorwald (12) studied the tissue reactions in guinea pigs following injection into one testicle of tubercle bacilli and the modification thereof by injection of an equal weight, 0.1 mgm., of smegma bacilli into the opposite testicle. They found that this procedure did not inhibit the development of tuberculosis caused by human tubercle bacilli; but when the two germs were simultaneously injected, the hyperaemia normally produced by the tubercle bacilli alone, apparent in six and intense within

twenty-four hours, failed to appear. Nevertheless, "the tubercle bacillus injection in one testis appears to have increased the deleterious effect of smegma bacilli in the other testicle."

INCEPTION AND OBJECT OF THE PRESENT WORK

The first report of progress in this work was made to the National Tuberculosis Association in 1928 (20) and the second in 1929 (21).

We cannot more clearly state the incentives for our enterprise than by *verbatim* quotation from the introduction to the first report:

While manipulating with cultures of a blue mould (which happened to be a prevailing contaminating organism in the laboratory) and of smegma bacillus one of us (de Savitsch) noticed that when smegma bacilli and mould-spores were mixed together in emulsion in approximately equal weights and were seeded on a solid culture medium, the smegma bacilli developed within three days while the spores did not grow for five or six days; whereas the spores when planted alone developed in twenty-four hours. When the bacilli were mixed with spores in the proportion of 5 to 1, in most cases the spores did not grow at all. When the spores were growing alone their development seemed to be checked in areas which were streaked with an emulsion of smegma bacilli. But the reverse was not true; the growth of bacillary cultures did not appear to be inhibited when sprinkled with spores of mould.

On considering these qualitative results, and others of confirmatory character, the suggestion at once occurred to determine whether smegma bacillus would show any inhibitory influence upon the development of its morphological similar, the tubercle bacillus.

Following the first three years of this work indispensable aid has been rendered by the technical assistance of C. P. Butler and of G. J. Duffner.

The strain of tubercle bacilli used by us had been isolated from human sputum by Dr. Corper, Director of the laboratory, about 1920.

It is here listed, according to the initial letter of its donor, as "TbcG." Subcultures of the bacilli have been propagated about monthly and, subjected to virulence tests several times a year, have been found to constantly cause tuberculosis in guinea pigs after subcutaneous infection with doses of 0.000,001 mgm. The dose of 0.001 mgm., often employed by us, habitually causes organ-tuberculosis in guinea pigs within three months, though life may persist for 200 to 300 days or more.

Two strains of so-called smegma bacilli have been available. One, which has been subcultured for several years in our laboratory, was first obtained from the department of pathology of the University of Chicago; thence its

origin has been traced to the Trudeau laboratory at Saranac Lake, whence the line of descent is broken. We call this strain, "Old Smegma" or "O. S."

Another culture of smegma bacilli was later obtained from the Hygienic Laboratory at Washington, D. C. It is thought to have emanated from a German laboratory. We know this culture as a product of the Hygienic Laboratory by the initials "H.L.S."

Both groups of bacteria in question in stained specimens closely resemble tubercle bacilli. They are acid-fast, though less strongly so than our tubercle-bacilli culture, and present the physical and cultural characters ascribed to "smegma bacilli." Planted on glycerin-agar or on Petroff's gentian-violet media, in the incubator at 37°C. they are growing well within three days as against two or three weeks for the tubercle bacilli.

Striking results of preliminary experiments led us to investigate the biological relationships of tubercle and smegma bacilli in various associations of their pure cultures both *in vitro* and *in vivo*.

Method: Our bacillary suspensions were made by grinding the weighed bacilli in a centrifuge-tube with a glass rod, after addition of a little 0.9 per cent NaCl. The same diluent was used for preparations of the milky emulsion. Subcutaneous inoculations were made in the lower abdominal wall, usually with a volume dose of 1 cc.

Our experiments utilized almost wholly young male guinea pigs weighing 250 to 400 gm. Careful autopsy was recorded in each case, including macroscopic estimation of lymph-node enlargement, and of the evidence of tuberculosis in spleen, liver and lungs, graded on a scale in which + represented minimal and ++++ maximal tuberculous infection.

Little reliance was placed upon apparent freedom from tuberculosis unless at least 90 days had elapsed since infection.

EXPERIMENTAL PROCEDURES AND RESULTS

1: The effect of simultaneous subcutaneous inoculations of guinea pigs in opposite sides of the body with virulent tubercle bacilli (TbcG.) 0.001 mgm. or 0.01 mgm., and smegma bacilli (O.S. or H.L.S.) 100 mgm.: In June, 1928, we reported an experiment of the preceding year in which 20 normal guinea pigs were inoculated on opposite sides with 0.001 mgm. virulent tubercle bacilli (TbcG.) and 100 mgm. smegma bacilli, half the animals with each strain of the latter. In addition, 10 control guinea pigs received each 0.001 mgm. TbcG. alone.

The results of the experiment may be summarized by stating:

those animals that received tubercle bacilli on one side and O.S. bacilli on the other, in 20 per cent of cases failed to develop any macroscopic signs of visceral tuberculosis. When the strain of smegma bacilli, H.L.S., was used the proportion of animals protected from visceral tuberculosis was 50 per cent. All controls infected with the same dose of tubercle bacilli died with generalized tuberculosis.

Normal guinea pigs inoculated with emulsions made from hard and greatly swollen lymph nodes of the protected animals showed, after three months, slightly positive signs of infection in some cases; in others none.

A year later the experiment was repeated in somewhat similar terms; and the conclusion was reached that, as for guinea pigs simultaneously inoculated on opposite sides with the dosages indicated, the development of tuberculosis in animals so treated may be wholly or partially prevented in approximately 50 per cent of the cases (21).

The complexity of the subject is indicated by the fact that still a year later, in repetition of the experiment, 10 guinea pigs inoculated as before showed little, if any, protection against tuberculosis.

2: The effects following inoculation of smegma bacilli alone: From the earliest accounts smegma bacilli have been classified with the nonpathogenic microörganisms. Nevertheless, statements are not uncommon that after massive inoculations anatomical changes resembling those of tuberculosis may be produced, though the tubercles are said not to caseate or to be infective.

In one of our experiments a control group of 10 guinea pigs was inoculated four times at weekly intervals with 10, 20, 40 and 100 mgm. of the H.L.S. culture. Local abscess was caused by repetition of the injections, but healed kindly when they were omitted. No shortening of the term of life occurred nor was there anatomical evidence of disease, except for more or less adenopathy of the regional lymph nodes. On several occasions in which control groups were treated with single doses of 100 mgm. of either of our strains of smegma bacilli, the final anatomical evidence was wholly negative for disease, with the exception of rather marked adenopathy, as mentioned. The latter lymph-node change should be expected by one who observes the intense inflammatory reaction, abscess-formation, necrosis and ulceration usually attendant in the area receiving a subcutaneous injection of 100 mgm. smegma bacilli;

it suggests the violence of reaction in "Koch's phenomenon," which may attend reinfection in tuberculosis. Yet the former alarming disturbance regularly subsides and the animal definitely recovers. Nevertheless, we must report two instances among hundreds of animals receiving smegma bacilli, including a fair number with no other treatment, in which the large dose of smegma bacilli was followed by an unusually generalized macroscopic tuberculosis which, at the time, was thought to represent the "spontaneous" or accidental disease of which we had had several illustrations.

3: Attempts to immunize guinea pigs against tuberculosis by subcutaneous inoculations with viable smegma bacilli: No recent attempt has been made in this direction. An experiment has already been reported in which 10 normal guinea pigs were inoculated subcutaneously with H.L. smegma bacilli in a series of four doses separated by intervals of seven days and in amounts of 10, 20, 40 and 100 mgm. Local abscess and ulceration occasionally developed which gradually healed. Fourteen days after the last injection and 35 days after the first, each guinea pig was inoculated with 0.001 mgm. TbcG. and a group of normal controls was treated in the same way. Brought to autopsy more than a hundred days after the last injections, the experimental pigs proved to be about as heavily infected with tuberculosis as the controls.

In the following year the experiment was repeated under similar terms except that the strain of smegma bacilli used was changed to O.S. instead of H.L.S. Of 7 experimental guinea pigs, two which died 280 to 308 days after their test inoculation with TbcG. showed *no* macroscopic visceral tuberculosis. This was a protection rate of more than 28 per cent. The 10 control animals were all heavily infected.

4: Treatment of established tuberculosis with single inoculations of H.L.S. bacilli in various doses at various intervals after inoculation with TbcG: In pursuing our plan to elicit the evidences for a biological antagonism between smegma and tubercle bacilli we shall quote again from the abstract of our work published in the *Transactions of the National Tuberculosis Association* (21).

Thirty-six normal guinea pigs were inoculated each with 0.000,1 mg. TbcG. (one-tenth the ordinary minimal dose). Twelve pigs were reserved for controls and were not treated further. The remaining animals were divided into four equal groups, A, B, C, D. At definite intervals after their inoculation with

TbcG. the six pigs of each group were inoculated each with viable H.L.S. bacilli as follows: A, interval 10 days after infection, dose of smegma bacilli 50 mgs.; B, interval 20 days, dose 60 mgs.; C, interval 30 days, dose 70 mgs.; D, interval 40 days, dose 80 mgs. *Results: Group A.* One of the 6 pigs, dying 319 days after inoculation with TbcG., showed extensive organ tuberculosis. Strange to say, the pig next most heavily infected, dying after 310 days, showed a spleen about normal in size and appearance. In one of the pigs which lived 253 days, no tubercles could be discovered, the only sign of disease being a great enlargement of the spleen. These animals, except the first mentioned, all presented a maximum degree of adenopathy. In short, there was no instance of absolute protection against tuberculosis, though there was extraordinary reduction in its extent as compared with the controls. *Group B:* One pig died within a week, the rest lived over 250 days after inoculation with TbcG. One of these was slightly, one moderately and three heavily infected with tuberculosis. *Group C:* The results here were of extraordinary character. Only one of the 6 pigs, which lived 115 days, presented fairly extensive organ tuberculosis. Of the remaining five, 2 were free from macroscopic organ disease (lived 126 and 272 days); 1 showed only enlargement of the spleen without tubercles (lived 121 days); 1 showed doubtful organ tuberculosis (lived 103 days); 1 which lived 390 days showed the unique combination of an apparently normal spleen with lungs somewhat heavily dotted with typical discrete hard tubercles. Adenopathy in this group was less conspicuous than in others. We shall later again have reason to suspect that an incubation period of 30 days, whether *in vivo* or *in vitro*, finds the tubercle bacillus in a peculiarly responsive metabolic condition toward smegma bacilli. *Group D:* Only 1 of the 6 pigs failed to show organ tuberculosis; this animal died within 76 days, too short a time for definite development of lesions. All the remaining animals were heavily infected except one which, after 239 days, showed but minimal organ tuberculosis.

The Controls: All twelve animals developed approximately maximal generalized disease except 2 which lived but 76 and 105 days and presented slight tuberculous infection.

5: Effect upon the infectivity of virulent tubercle bacilli when these are mixed with smegma bacilli and cultivated on the same solid medium: Some of our most positive evidences for an inherent biological mastery of smegma bacilli over tubercle bacilli were witnessed in procedures through which the germs, thoroughly commingled with an excess of TbcG. as high as 5 to 1, were cultivated on the same medium and after various periods of incubation at 37°C. were then emulsified and inoculated in large doses (10 mgm.) into normal guinea pigs.

Postmortem examination revealed an extraordinary difference as

regards the presence and extent of tuberculosis in two groups of animals according to the period of incubation of the infecting bacillary mixtures. Animals which had been inoculated with mixed cultures, incubated 27 days, all were affected with visceral tuberculosis, though manifestly the development of the disease had been more or less decidedly retarded. On the contrary, of those guinea pigs inoculated with mixed cultures that had been incubated 43 days, 50 per cent were completely free from macroscopic evidence of visceral tuberculosis and in a further 33 per cent the extent of disease was distinctly limited.

We were inclined to interpret these results as due to a lethal influence upon the tubercle bacilli of incubation in the association described.

But in the following year this interpretation was apparently overturned as the result of evidence set forth in the next section.

6: Comparison of infectivity in mixed cultures of smegma and tubercle bacilli which had been incubated on solid media at 37°C. for 30 and 60 days, respectively (21):

(*1*) *Infectivity of bacillary-mixtures incubated 30 days:*

The mixtures with each strain were made in 4 proportions by weight, namely, smegma bacilli: tubercle bacilli, 1:1; 1:2; 1:3; and 1:5.

After incubation at 37°C. had continued 30 days, emulsions were prepared from which 32 young male guinea pigs were inoculated, each with a dose of 10 mgs. of bacilli, 4 pigs being devoted to each proportion of the bacillary mixtures.

Of 19 pigs which had been submitted to autopsy 114 to 335 days after inoculation, 10 had proved tuberculosis-positive (one in very slight degree) and 9 were macroscopically negative; the remainder were devoted to immunity tests.

(*2*) *The mortality rate in guinea pigs inoculated with mixed cultures which had been incubated at 37°C. for 60 days:*

After lapse of 60 days in the incubator fresh emulsions were prepared from the remaining mixed-cultures and inoculations were made in another group of guinea pigs, all procedures being, as far as possible, exactly similar to those already described. As in the previous experiment, 30 pigs were available for final analysis. The results were radically different. Only two of the animals lacked macroscopic lesions of tuberculosis and this only 61 and 81 days after inoculation, periods too short to exclude possibility of infection. The visceral tuberculosis was slight in 3 pigs dying after 99, 157 and 203 days but in all the rest tuberculosis was general and more or less advanced.

This experiment proves the viability of the tubercle bacilli in mixtures incubated for 60 days; that the smegma bacilli also lived was indicated by growths within 2 to 4 days in subcultures made at the end of 60 days' incubation.

Comparing these two experiments, we seem justified in concluding that in pure cultures of smegma and tubercle bacilli, mixed and incubated together for 30 days at 37°C., the pathogenicity of tubercle bacilli is held in abeyance or abolished in a large measure, probably again to be recovered on prolonging the incubation.

7: Lack of specific immunity in guinea pigs proved refractory to culture-mixtures containing tubercle bacilli: In the experiment in which inoculation was performed with mixed cultures that had been incubated 30 days, about half the animals apparently had failed to develop tuberculosis. Eleven guinea pigs remained alive in fair to good condition 335 days after their inoculation with 10 mgm. of bacillary mixtures, and it was obviously important to determine their immunological status respecting tuberculosis. It was purposed to test their immunity by reinoculation of each with 0.001 mgm. of a pure culture of TbcG. The reinoculation was administered 341 days after the original infection; at the same time 10 normal guinea pigs were given a like dose as controls.

The 11 animals of the experimental group survived their reinoculation an average of 127 days. Nine of them showed more or less advanced visceral tuberculosis; 2 cases were doubtful.

The 10 normal control animals infected with 0.001 mgm. TbcG. survived an average of 196 days, as compared with 127 days for the experimentals, and all were far advanced in general tuberculosis with the exception of one dying in 70 days with slight infection.

8: A general examination of the relation between the periods of incubation of mixed bacillary cultures and their infectivity for guinea pigs: In the experiments described in section 6 solid Petroff culture media were heavily seeded from opaque emulsions of mixed cultures, in which the content in tubercle bacilli was generally in notable excess. With the view of eliminating accidental errors still another series of five separate experiments was projected, each carried out essentially as described above. The key-determinant in each was the period of incubation of our mixed cultures at 37°C. This period for the respective experiments was: *a*, 20; *b*, 30; *c*, 40; *d*, 50; *e*, 71 days.

In each of the five experiments the mixtures of H.L.S.:TbcG. were planted in 9 different proportions, namely, 1:1; 1:3; 1:5; 1:7; 1:9; 3:1; 5:1; 7:1; 9:1. In every experiment, at the termination of the appropriate period of incubation, separate bacillary emulsions were prepared to furnish a uniform dose of 10 mgm. of each of the nine different bacillary mixtures.

Each experiment employed 27 young male guinea pigs, 3 of which were devoted to each of the 9 bacillary proportions, except that 36 animals were allotted to *b*, 4 for each proportion.

Our final calculations were based on autopsies following spontaneous exitus and excluded all cases surviving inoculation less than 100 days.

TABLE 1

Influence of duration of incubation at 37°C. on the infectivity of mixed cultures grown on solid media

INDEX OF EXPERIMENT	DURATION OF INCUBATION	NUMBER OF GUINEA PIGS INOCULATED	NUMBER OF ANIMALS TUBERCULOSIS-FREE AT AUTOPSY	PER CENT OF TUBERCULOSIS-FREE ANIMALS	NUMBER OF ANIMALS SHOWING SLIGHT OR DOUBTFUL INFECTION
	days				
a	20	23	2	8.7	2
b	30	34	6	17.6	2
c	40	24	5	20.0	5
d	50	23	3	13.0	2
e	71	26	1(?)	3.8(?)	0

A summary of results is presented in table 1. Thus, in experiment *a* the mixed cultures had been incubated at 37°C. for 20 days when used for inoculation. Within 100 days 3 guinea pigs died and one was lost, leaving 23 which succumbed from time to time up to 330 days after inoculation. Two animals, or 8.7 per cent, were found free from tuberculosis, though two others also showed very slight or doubtful infection, as indicated in the last column. It will be noted that the suppression of toxicity in mixed cultures, as the result of incubation, is quantitatively less marked than in previous experiments; and we find that the suppression of tuberculous infectivity in the mixed cultures reaches its peak after about 40 days' incubation, when 20 per cent of the animals are completely negative for tuberculosis and a similar proportion show doubtful signs of the disease.

When incubation of the mixed cultures was continued for 71 days all of the 26 guinea pigs inoculated developed tuberculosis, except one

dying with pneumonia in 222 days and recorded as doubtful; this animal had received smegma bacilli TbcG., 3:1; its two companions with the same dose were positively infected.

Although care was used to thoroughly grind and evenly emulsify each mixed culture preparatory to animal inoculation, the 3 or 4 infecting doses of 10 mgm. each drawn from the same tube had a biological effect determined rather by the preceding period of incubation than by the ratio of the two germs when planted. Thus, in experiment *c*, of 3 guinea pigs, each inoculated with 10 mgm. of a mixed culture, seeded in the proportion H.L.S.: TbcG., 9:1, two failed to develop tuberculosis while one succumbed to maximal infection; when the proportions were reversed, with the tubercle bacilli in excess, the guinea pigs all died of pneumonia after an average of 275 days, but only one of them showed any suspicion of tuberculosis.

The main question with which this series of experiments started seems to have been answered; failure of our mixed cultures to infect could not have been due to complete destruction of the tubercle bacilli. Further inquiry into the conditions of detoxication will be deferred until the very different results from cultivation on a liquid medium have been considered.

Presumably, detoxication of our mixed cultures should find its explanation in metabolic changes incident to growth of the respective germs; none the less, it seemed advisable to ascertain whether fresh mixtures of the two forms of bacilli made from their separate pure cultures can themselves present evidences of detoxication. This question appears to be definitely answered, for the conditions imposed, in the next section.

9: The infectivity of freshly-mixed pure cultures of smegma and tubercle bacilli: Four different mixtures were prepared from pure cultures of tubercle bacilli and smegma bacilli. Each infecting dose consisted of 1.0 cc. of physiological salt solution holding in suspension a constant of TbcG., 0.001 mgm., with one of four different dilutions of smegma bacilli (H.L.S.) containing respectively, 0.001, 0.01, 0.1 and 1.0 mgm.

That is, the constant infecting dose of TbcG., 0.001 mgm., was mixed with a series of H.L.S. dilutions, in which at one end the two germs were present in equal weights and at the other the smegma exceeded the tubercle bacilli 1,000 times. Fifty young male guinea pigs were devoted to this investigation; 10 were appropriated to each of the four

bacillary mixtures, and, besides, 10 were inoculated, as controls, each with 0.001 mgm. TbcG. The results of the experiment left no room for doubt; in three of the groups inoculated with bacillary mixtures the postmortem appearance duplicated that in the controls. The same thing was true for the remaining group except that the diagnosis of tuberculosis was complicated with pneumonia and other changes.

The evidence, then, is positive that we cannot account for the assumed protective power of smegma bacilli against the virulence of tubercle bacilli as the result of mere antidotal action. Incubation together of the two germs, *in vivo* or *in vitro*, seems necessary to modify virulence. Our quest was therefore continued with modification of method as follows:

10: Modification of infectivity in mixed cultures of smegma and tubercle bacilli when grown upon synthetic, nonprotein liquid media: It was our intention to find whether mixed cultures of smegma and tubercle bacilli would repeat, when grown on liquid media, the modification of infectivity we have already considered. By such means, also, soluble products of metabolism could be separated from the bodies of the germs and each studied independently. Our liquid culture medium was a nonprotein solution prepared according to the well-known formula of Long, but somewhat modified as advised by Dr. N. Uyei, chemist of the laboratory (National Jewish Hospital).

In the first experiment in this series bacillary emulsions were prepared from cultures of TbcG. and H.L. smegma and mixed in three proportions, namely, H.L.S.: TbcG., 1:1; 1:3 and 1:5. Numbers of Petroff tubes were seeded with each proportion and were incubated at 37°C. for 26 days. Emulsions were then prepared, representing each of the bacterial mixtures, and plants were made upon the liquid synthetic medium, three flasks for each proportion. The cultures grew readily; and, after 14 days' incubation (making a total of 40 days' incubation from the beginning), one flask of each proportion of the mixtures was removed, and its growth shaken down and separated from the liquid medium in a centrifuge. Our common procedure was to wash sedimented bacterial mixtures several times by decantation, suspension in physiological saline solution and centrifugation. The bacterial sediments were then ground with saline solution, 10 mgm. to 1 cc., and stored in rubber-capped vials in the refrigerator. The viable bacillary mixtures thus obtained were inoculated into normal guinea pigs in doses

of 10 mgm. Six guinea pigs were devoted to each proportion of three bacillary mixtures,—a total of 18 animals.

It happened that the ensuing winter was one of unusual severity, which may have played a part in an epidemic of pneumonia which invaded our animal room. In our résumé of results, 2 guinea pigs must be rejected by reason of early death and one had been lost; 5 lived from 55 to 95 days before succumbing to pneumonia; these might have shown at least splenic tuberculosis, but autopsies showed both spleen and liver practically clear in each case. Another, pneumonic after 122 days, showed slight evidences of tuberculosis in spleen and liver. But the remaining 9 guinea pigs, living 101 and 155 to 303 days after inoculation, all showed advanced generalized tuberculosis.

The results described seem clearly to indicate that the development of tuberculosis was retarded up to a period of about 120 days following inoculation, but that the disease was greatly accelerated at some period between 100 and 150 days after infection.

As in previous experiments, the mixtures containing, when seeded, the higher proportions of tubercle bacilli showed no excess of virulence.

In the preceding experiment the bacillary mixtures while growing on liquid media were incubated only for 14 days; this was conceivably too short a time for the development of the changes leading to detoxication of the tubercle bacilli.

The remaining flasks were kept in the incubator a full 30 days; their growths were then centrifugated and prepared for inoculation.

Inoculation was performed, as before, on 27 guinea pigs in three groups of 9 each, in which the dosage was 10 mgm. of mixed culture assumed to contain H.L.S.: TbcG, 1:1, 1:3 and 1:5. Seven of the animals were later unavailable for various reasons, leaving a total of 20. Ten of these guinea pigs died of pneumonia 54 to 82 days after inoculation; there was no evidence of tuberculosis except for enlargement of the spleen in one. Two more died of pneumonia, but were free from tuberculosis 217 to 233 days after infection. The remaining 8 animals remained well and, 247 days after their inoculation, five of them were treated with a subcutaneous injection of 0.01 mgm. TbcG. each as a test of immunity. Each of these five died with generalized tuberculosis 100 to 160 days after this reinfection, except for one which lived but 14 days. These results confirm the negation of immunity deduced from analogous experiments using Petroff's medium.

There still remained alive 3 guinea pigs which had received the orig-

inal inoculation with mixed cultures, but no reinfection. The three guinea pigs were chloroformed 652 days after their inoculation. The first two were macroscopically free from tuberculosis; the third animal (H.L.S.:TbcG., 1:3), showed only slight enlargement of the spleen.

Once more we repeated the experiment based on the cultivation of bacillary mixtures upon the liquid medium. But on this occasion there was no preliminary cultivation upon a solid soil; rather, the pure cultures of bacilli that had been mixed and ground in the usual proportions were directly planted upon Long's medium and incubated at 37°C. for 60 days. The flasks were then removed and stored at room temperature for 14 days, when the various mixed cultures were separately washed and injected into 30 guinea pigs, 10 animals receiving a dose of 10 mgm. of each proportion.

Twenty-seven animals survived for study; 14 of them, dying or killed 300 to 440 days after inoculation, not one showed definite macroscopic evidence of visceral tuberculosis or of lymph-node swelling. The other 13 guinea pigs were allowed to rest for 60 days following their inoculation with the bacillary mixtures, but were then reinoculated in the opposite (right) groin, each with 0.01 mgm. pure culture TbcG. Twelve of these animals repeated the histories of similarly reinoculated pigs, death from general tuberculosis apparently being hastened as compared with controls. The one remaining animal, for unknown reasons, wholly escaped infection.

We cannot but entertain the suspicion that cultivation of the mixed cultures for 60 days upon the liquid medium had been fatal to their content of tubercle bacilli, notwithstanding the contrary evidence from cultivation on solid media. It is expedient to defer a critique of this matter until after presentation of the next section.

11: Nature of the nonpathogenic association of smegma and tubercle bacilli: Interpretation of our results requires a conception of the mutual relations of the saprophytic and parasitic acid-fast bacilli, when grown together in mixtures in which, at the outset, the pathogen may form 90 per cent of the total, and yet after a certain period of incubation, when inoculated in large doses, prove harmless for guinea pigs.

Our general results suggest that the incubation of tubercle bacilli at body temperature for about 30 days, either *in vivo* or *in vitro*, may render them peculiarly susceptible to environment. Thus, in section 4,

animals inoculated with smegma bacilli 30 days after infection with tubercle bacilli developed a lower incidence of tuberculosis than at any other interval.

Repeatedly we have found mixtures of the two forms of bacilli, after incubation together on solid media for 30 or 40 days, to be largely innocuous for guinea pigs. The obvious explanation, which assumes the death of the tubercle bacilli in the culture, is rendered doubtful by the fact that pathogenicity is restored by prolonging the incubation. Also, we should expect that normal guinea pigs inoculated with 10 mgm. of germs consisting largely of dead tubercle bacilli should develop decided resistance against reinoculation with virulent bacilli (5). This we have repeatedly proved does not occur under our conditions (*vid.* sections 7 and 10).

At first we were inclined to the opinion that incubation of the two forms of bacilli together might lead within about 40 days to a sort of linkage between them, resulting in a nonpathogenic union which became resolved on sufficiently prolonging the incubation. Nevertheless, cultures of bacillary mixtures grown on Long's liquid medium do, as related above, invariably permanently lose tuberculous pathogenicity after incubation for 30 to 40 days. We may suppose that a metabolic product of growth of smegma bacilli inhibits or kills the tubercle bacilli. On the whole, this would seem the safest provisional conclusion.

The duration of incubation being the controlling factor in determining the infectivity of mixed cultures, it seems plausible that the functional complexes of presumably nonpathogenic mixed growths might be resolved by subculturing them on fresh media after various periods and testing the resulting growths for pathogenic action by animal inoculation. Such an investigation was carried out recently, seven years after beginning the original experiments, and an outline of results will be given, though the work is still most incomplete.

12: Attempts to resolve the functional attributes of mixed cultures of smegma and tubercle bacilli: In the previous work, inoculated animals were usually allowed to die spontaneously, often after a year or more, but in the experiments to follow the guinea pigs were killed, usually by electric shock, within a period of 3 to 5 months after inoculation.

A notable general difference distinguished the pathological effects of animal inoculation in this series of experiments from those of previous years; we believe this difference to depend on biological changes in the

smegma bacilli alone. The pathological effects referred to, while not universal, were distributed through 7 classes of manipulation involving, usually, 10 guinea pigs each; they consisted in the formation of peritoneal adhesions, very rarely acutely inflammatory, manifested as a firm local union between the omentum and abdominal wall, slight matting of the upper intestines, or fine sheets of membrane between the liver and diaphragm. Withal, these formations frequently could have easily escaped attention.

The first experiment of the present group was a repetition of previous ones, in which it was found that when mixed cultures of smegma bacilli and tubercle bacilli, the latter largely in excess, were incubated at 37°C. together on Petroff's gentian-violet medium for 35 days, the growth proved nonpathogenic for guinea pigs inoculated subcutaneously in doses of 10 mgm. In our recent experiment, the mixed cultures were in two proportions, 1:3 and 1:9, the TbcG. being in excess, and the guinea pigs were killed about 114 days after inoculation. All 10 animals were recorded as tuberculous, though in nearly half the only abnormal visceral sign was enlargement of inguinal and iliac lymph nodes; organ disease, when present, was limited to the spleen. The impression was gained that about half the subjects were cured or on the way to cure of tuberculosis. As before, no great difference distinguished the effects of the two bacillary proportions.

The second experiment of the series used as culture medium Long's synthetic fluid and the incubation period, which should have been shortened, was unfortunately prolonged to 43 days. The 10 animals, killed 112 to 115 days after inoculation, all proved free from positive signs of tuberculosis, though the presence of peritoneal adhesions witnessed infection. We are indebted to Dr. M. L. Cohn of this laboratory for numerous determinations of the pH of our culture media; in the present case it was 7.6 before and 8.50 to 8.55 at the end of incubation.

Our third experiment was a repetition of that in which mixed cultures were incubated on Petroff's solid medium for 71 days. Autopsies performed 95 to 101 days after inoculation showed 8 out of 10 animals to have visceral organ tuberculosis, an incidence much higher than when the incubation period was 35 days.

A fourth experiment in which this same period of incubation (71 days) was used on Long's liquid, showed that animals inoculated with the growth proved free from tuberculosis after 103 days, though peritoneal adhesions were present. Dr. Cohn found the pH to be raised from 7.6 before to 8.86 in 3 flasks and 8.12 in 1 flask after incubation.

We now come to the distinguishing feature of this recent work, namely, the use of subcultures of bacillary mixtures for animal inoculation.

In our fifth experiment the bacillary mixtures were incubated on Petroff's medium for 35 days (under which conditions the resultant growths had previously lost much of their power to convey tuberculosis); but, instead of using the growths for animal inoculation, transplants were made to fresh Petroff tubes, on which the cultures grew and were incubated anew for 47 days. From these growths 4 guinea pigs were inoculated in the usual way. When killed and examined 96 and 97 days later, these animals proved to be *free from tuberculosis*, although the usual peritoneal adhesions were present. We may infer that the tubercle bacilli had either completely died out in the tubes of transplant or had entered a nonpathogenic union.

The next, sixth, experiment resembled the last except that the transfer from Petroff's was made to Long's liquid, on which cultivation for 47 days gave growths which proved nonpathogenic. Dr. Cohn found the alkalinity of the fluid raised from pH 7.2 to 8.8 in a flask containing the smaller proportion of TbcG., and to pH 8.78 and 8.80 in flasks containing the larger proportion.

In the last, seventh, experiment to be noted, the primary incubation was on Long's liquid for 43 days; the bacillary mixtures were then transferred to Petroff's medium for 47 days, and then inoculated into guinea pigs. The results were negative for tuberculosis, but the usual peritoneal adhesions were found and also, for the first time, there was evidence of skin necrosis at the sites of inoculation and an occasional subcutaneous abscess was present without involvement of the regional lymph nodes.

Therefore, it seems probable that, as far as these experiments go, they imply that the curious lack of infectivity witnessed in some bacillary mixtures within 40 days of incubation, and in all mixtures cultivated for that time on a fluid medium, is due finally to destruction of the content of tubercle bacilli.

13: Attempts at prophylactic immunization through killed or attenuated bacillary cultures: It was an obvious thought to use the material resulting from our cultures upon fluid media for prophylactic and therapeutic inoculation. Sufficient material of each of the three mixture ratios described in section 10 was suspended in physiological saline solution, and heated to 50°C. for 30 minutes. Subcultures made after heating,

and incubated at 37°C., showed no growth for 15 days but were positive in 19 days. Before beginning inoculations, the mixed cultures were emulsified in normal salt solution to which was added carbolic acid to 0.5 per cent. Twenty-four guinea pigs were given, at weekly intervals, three subcutaneous injections of one of the presumably killed bacillary mixtures. The inoculations were made on alternate sides (left, right, left) in ascending doses (5, 10 and 15 mgm.).

Thirty days after the last prophylactic inoculation, the sites of inoculations having returned to normal appearance, the 24 experimental guinea pigs together with 5 normal controls were given subcutaneously on the left side injections of pure culture TbcG., half with dosage of 0.001 mgm. and half with 0.01 mgm. The results were significant; although only three of the experimental guinea pigs revealed positive evidence of protection, the average length of life in the experimental animals was over 215 days, as against an average life of 187 days for the controls.

It should be said that the test injection of the experimental guinea pigs with tubercle bacilli was followed by local development of the characteristic nodule of infection; and it is of interest to observe that *no acceleration of nodule-formation* attended this infection in our experimental animals. Such acceleration of nodule-formation is a constant accompaniment of *reinfection* in tuberculous animals.

The work of Branch and Cuff (5) and of others would suggest, as agents of the partial prophylaxis observed by us, the dead bodies of tubercle bacilli, which at the beginning of incubation greatly preponderated in our bacillary mixtures. We have already noted the lack of acceleration in formation of the nodule formed by viable bacilli following the injection of nonviable antigen; interesting, if so simple a test determines the viability of a primary antigen.

14: Therapeutic treatment of tuberculous guinea pigs with various products of smegma bacilli: Indubitable evidence has been offered that living "smegma" bacilli can vitally antagonize tubercle bacilli either *in vivo* or *in vitro*, and that in the former environment they may either prevent development of experimental tuberculosis or check its progress when under way. Obviously, it is of prime practical importance that the effective agent against tuberculosis, which apparently resides in the living smegma bacillus, be isolated in some product which is incapable of reproduction.

In this endeavor the smegma bacilli (strain H.L.S.) were grown on Long's synthetic medium for 40 to 60 days. The bacilli were separated from the culture fluid by centrifugation. The washed bacilli were killed by boiling, then emulsified in definite concentration in 0.9 per cent NaCl and preserved in rubber-capped bottles: this preparation of the dead bacillary bodies we know as "smegma residue."

The culture liquid from which the bacilli were removed was in the later work passed through Berkefeld candles and then stored aseptically in ampules. We call this "smegma filtrate," or "Smegmin."

a: A preliminary survey of antituberculosis efficiency of smegma bacilli and their products was made on 40 young male guinea pigs divided into 4 equal groups; each animal was infected subcutaneously in one groin with 0.001 mgm. virulent tubercle bacilli (TbcG). Simultaneously in the opposite groin each group was inoculated as follows: (1) viable smegma bacilli (H.L.S.) 100 mgm.; (2) heat-killed smegma bacilli (smegma "residue") 100 mgm.; (3) filtrate from growth of smegma bacilli (Smegmin) 1 cc.; and (4) control group infected only with TbcG.

Results: The controls all died with generalized tuberculosis within 115 to 321 days after infection. In view of our previous experiments, (section 1), we were chagrined to find that all of our group (1) died with tuberculosis within 337 days. The same fate attended the residue group (2) with the exception of one guinea pig that lived 399 days and *showed no positive macroscopic sign of tuberculosis.*

In the filtrate or Smegmin group (3), 3 guinea pigs, dying 113 to 169 days after infection, *showed no positive signs of tuberculosis.*

We shall later again consider therapeusis with Smegmin.

We shall now present only in abstract much of the work done in this field.

b: Treatment of established tuberculosis by inoculation with heat-killed previously incubated mixtures of smegma and tubercle bacilli: Thirty-two normal young guinea pigs were inoculated, half with 0.001 mgm. and half with 0.01 mgm. TbcG. Eight of these were set aside as controls and the remaining 24 were used for treatment.

Thirty-six days after infection, treatment was begun with dosages, determined after preliminary trials, of 0.1 mgm. and 0.01 mgm. of bacillary residue at weekly intervals.

We conclude that the heat-killed cultures of mixed smegma bacilli and tubercle bacilli possess no constant definite value against tuberculosis.

c: Therapeusis of tuberculosis by inoculation with the soluble products of the growth of mixed cultures on liquid media: Tuberculo-Smegmin: The fluid, con-

taining products of growth of the mixed cultures of smegma and tubercle bacilli, as described in section 10, was separated by centrifugation, at times filtered through Berkefeld cylinders, and stored in ampules at 5°C. It was used in the treatment of young guinea pigs which had been infected about 30 days before by subcutaneous injection of TbcG. in doses of 0.001 mgm. or 0.01 mgm. The "Tuberculo-Smegmin" fluid was administered subcutaneously in the opposite groin at weekly intervals in doses of 0.001 cc. to 0.01 cc. The total number of doses was fifteen.

Results: Animals treated with Tuberculo-Smegmin from mixed cultures incubated at 37°C. for 60 days died as soon and with as extensive disease as the controls. But tuberculous animals treated with Tuberculo-Smegmin resulting from an incubation period of about 30 days showed in one-sixth of the cases very marked protection.

d: Treatment of tuberculosis in guinea pigs with the bacterial filtrate, "Smegmin:" In spite of the confusing irregularity which attended our efforts in therapeusis, there had appeared substantial evidence that the soluble product from the metabolism of smegma bacilli alone on the liquid nonprotein medium contained principles potent for our purpose.

It soon developed that the technique of dosage with Smegmin was a complex performance. A single dose of 1 cc. of the filtrate caused no disturbance in a tuberculous guinea pig; but, when a group of such subjects was treated serially with 0.01 to 0.05 cc. at weekly intervals, we were impressed with somewhat of an analogy to tuberculin in the reactions. The experimental animals might thrive notably well for six weeks, and then decline faster than the controls. This course was apparently more rapid with shorter intervals of treatment. Finally, the plan was adopted, with good results, of regulating the injections according to the current clinical condition of the guinea pig, as determined by its behavior and especially by its body weight.

We are greatly indebted to Doctors Long and Seibert, then of the University of Chicago, for providing us with quantities of smegma filtrate or "Smegmin," a name independently adopted by them. This preparation, as judged by its color, was more concentrated than ours. It probably corresponds to our "O. S." strain of Smegmin, whose parent stock had been given us by Doctor Long. Doctor Seibert had prepared the Smegmin from cultures grown on Long's nonprotein liquid medium at 37°C. for about 8 weeks. They were then filtered with aseptic precautions through Berkefeld candles and the bottled filtrates expressed to us.

Two series of experiments were carried out with the use of this preparation in the treatment of guinea pigs infected with tubercle bacilli 30 days previously.

In one experiment the dosage of Smegmin was 0.05 cc. given subcutaneously at intervals of 7 days. In the other series the dosage was 1 cc., and the

intervals between the injections ranged from 13 to 25 days. No positive conclusions can be drawn as to the effect of treatment upon the course of the disease, though its extent was somewhat less under the larger doses than in the corresponding controls.

e: Evidence of amelioration or cure of experimental tuberculosis in guinea pigs under serial inoculations with Smegmin from bacilli of strain "H.L.S.": Our experiment involved 30 young male guinea pigs, all of which received a subcutaneous injection of TbcG., equal numbers being infected with 0.001 mgm. and 0.01 mgm. Ten animals were reserved as controls, and 20 began their dosage with 0.05 mgm. Smegmin 34 days after their infection, repeated at weekly intervals, or longer, according to clinical condition.

Of the 10 experimental guinea pigs which had received 0.01 mgm. TbcG., none showed complete immunity, but in one animal, dying 115 days after infection, both spleen and liver were free from signs of tuberculosis, though the lungs were moderately affected; another after 174 days showed considerable pulmonary involvement, but little or none of the liver and spleen. Of the 10 experimental guinea pigs which had received 0.001 mgm. TbcG., no less than four, dying 148, 203, 214 and 481 days after their infection, showed, the first and last, *no macroscopic signs of tuberculosis whatever*, while the other two revealed only a slight suspicion of visceral tuberculosis. It might be suspected that, with the comparatively small dosage of 0.001 mgm., the bacilli might have been wholly omitted from certain dosages. But this suspicion is completely refuted by the fact that each of the 30 animals developed at the site of inoculation the typical primary nodule of infection which pursued its usual course.

The 10 control guinea pigs all died with generalized tuberculosis after approximately the same length of life as the experimentals, which themselves were apt to succumb to pneumonia.

Two years later, repetitions of this procedure, employing Smegmin resulting from bacillary incubation periods of 19, 33 and 61 days, gave very little encouragement for therapeutic exploitation.

SUMMARY

1. It has appeared that the saprophyte, the smegma bacillus, introduced into the body at the same time as, but independently of, the parasite, the tubercle bacillus, in about half the cases may, with certain proportions of the two germs, completely prevent the development of tuberculosis (section 1).

2. When the experimental disease is well under way, especially at a period of 30 days following infection, the inoculation of living smegma

bacilli has not been capable of inhibiting the pathological process to any degree (section 4).

3. When the pure cultures of the two germs are intimately mixed and incubated at 37°C. on the same solid medium for an optimum period of 30 to 40 days, guinea pigs may be unaffected by the inoculation of great doses of a germ mixture which, when planted, contained as much as 90 per cent of virulent tubercle bacilli.

4. Mixed cultures of smegma and tubercle bacilli, whose incubation on solid media has been prolonged to 60 to 70 days, are found again to be completely infective.

5. Mixed cultures on Long's liquid synthetic medium, when incubated 30 days or more, appear permanently to lose power to infect with tuberculosis (sections 10 and 12).

6. Guinea pigs, which have thus proved refractory to growths from either media, are not thereafter immune from tuberculosis, since they develop the disease when reinoculated with pure cultures of tubercle bacilli; indeed, the reaction may resemble that of tuberculous allergy in animals which, without reinfection, would possibly not have died of tuberculosis (section 7).

7. In guinea pigs, recently infected with tuberculosis, the subcutaneous administration of either the heat-killed, washed bodies of smegma bacilli or of the "Tuberculo-Smegmin" resulting from the growth of mixed cultures on liquid media, occasionally manifests antituberculosis properties. But a more promising therapeutic agent is found in "Smegmin," a product of the growth of smegma bacilli on a liquid medium for approximately 30 days, administered with precautions familiar in the use of tuberculin (section 14).

CONCLUSIONS

1. Through a period of nearly ten years we have repeatedly studied the vital relations between a constant strain of virulent human tubercle bacilli and one of smegma bacilli. The latter organisms, injected subcutaneously into guinea pigs in amounts of 10 to 100 mgm., cause local abscess-formation, and with the larger doses violent local inflammatory reactions and necrosis. The outcome is usually wholly benign, leaving no trace except moderate adenopathy of regional lymph nodes. Like others, we have occasionally seen massive dosage followed by generalized tubercle-formation.

2. Within the past year, pure cultures of the original strain of smegma

bacilli, injected into guinea pigs in doses of 10 mgm., are prone to be followed by indolent peritoneal adhesions.

3. We suspect, but have not proved, that the detoxication of bacillary mixtures, temporary on solid but permanent after about 30 days on liquid media, is due to Smegmin, a metabolic product of smegma bacilli.

4. Smegmin, given to tuberculous guinea pigs subcutaneously in single large doses, appears harmless, but in repeated small doses may suggest the toxic qualities of tuberculin.

5. The occasional therapeutic value of Smegmin noted in this communication would seem to make desirable a further experimental study of this agent.

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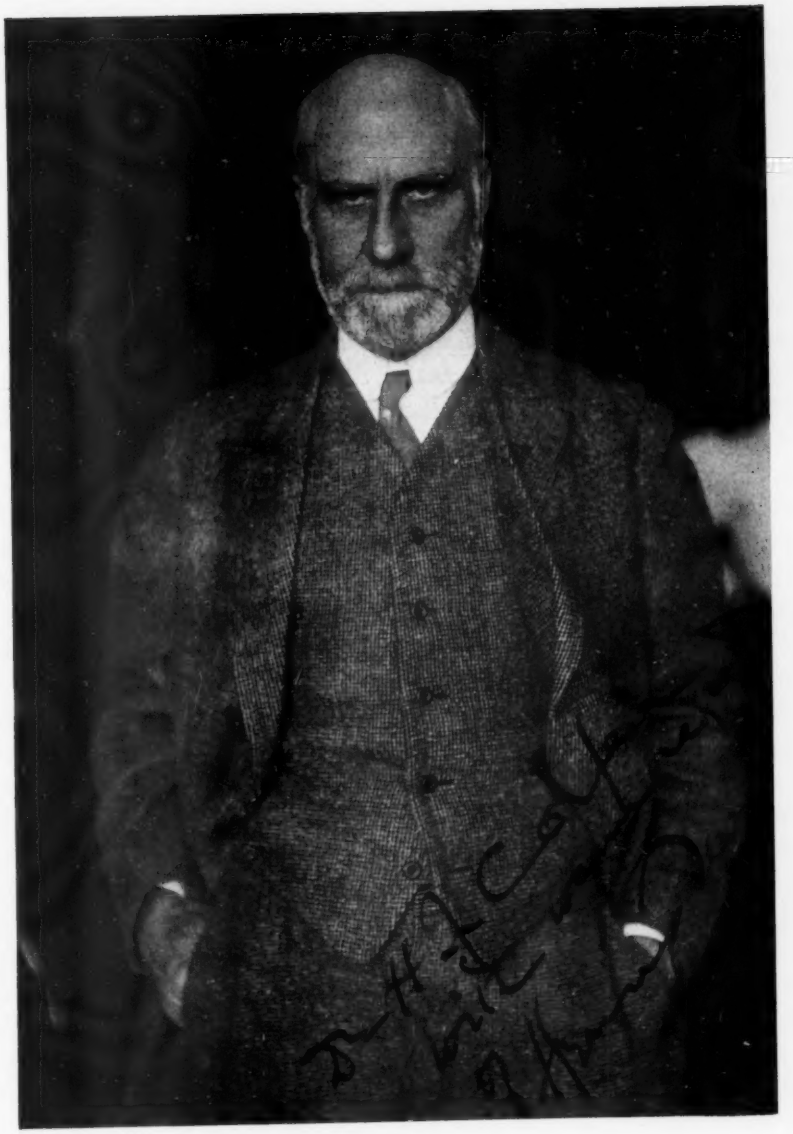
Henry Sewall

1855-1936

A physician's greatness is measured by his generosity to his colleagues and to his fellow-men. Henry Sewall measured up to the full in both of these requirements. He never neglected a patient, regardless of means; he never neglected his scientific studies, regardless of his health or the urgency of other demands; and he always found time to aid a charitable and just cause, even to performing the often menial task of finding the needed pecuniary wherewithal that spelled success for this cause. His intimate professional and scientific friends ranked from those crowned with success to those who were struggling for an education without means. To him even an unkind word to an experimental animal was unwarranted and to be looked upon with disdain. He was concerned with their welfare; without it success was futile. To those who did not at first understand his aims, he was a tenacious, persevering, and trying taskmaster; but warmth grew from acquaintance and association. He was a teacher whose lessons were never to be forgotten. His name among scientific and professional men would immediately lead to the recounting of lessons taught which had never been forgotten but were verified by the lapse of time. His demands for work were meagre. He could be content with a bench or a room, so long as his colleagues were there for communion. He was avid to learn the new and the fine. He didn't believe in retirement. A vacation was a means to catch up with writing and reading. Records were important and details essential, even to the description of his own final illness:—his colleagues should know the causes of his decease.

Dr. Sewall's influence not only pervaded Colorado but was national. In Colorado his colleagues and collaborators (1) included S. B. Childs (roentgenologist), Cuthbert Powell (obstetrician and gynaecologist), C. F. Hegner (surgeon), Robert Levy (otolaryngologist), W. C. Mitchell (health), Saling Simon (tuberculosis), James J. Waring (internal medicine), Gerald B. Webb, and many others prominent in scientific and clinical medicine in this State. Among his close friends and colleagues nationally were numbered Wm. J. Mayo, H. E. Robertson (Mayo



Clinic), Florence Sabin (Rockefeller Institute), V. C. Vaughan and F. G. Novy (University of Michigan), George M. Kober, Allen K. Krause, and others too numerous for mention here.

A Wesleyan University graduate in 1876, he greatly admired his instructor, Professor Henry Newell Martin, under whom he became Assistant in the newly founded Johns Hopkins University at Baltimore. Having taken his Ph.D. in 1879, a year in Europe brought him under the influence of Carl Ludwig and Michael Foster (2), and in 1882 he was invited to the University of Michigan to found and serve as head of the Department of Physiology. Victor Vaughan, in his *A Doctor's Memories* (3), recalls interesting experiences with Sewall, and recounts his failure as a prophet in predicting the success of such pupils as Mall, Mayo, and Courtney from student abilities in physiology, but says that "as a physiologist Sewall has had but few equals." Twenty years after Sewall was compelled to give up his teaching at Ann Arbor in 1889 (by symptoms of pulmonary tuberculosis which became suddenly evident in 1885), a delegation of learned Frenchmen introduced themselves to Dr. Vaughan by saying that they had journeyed to Ann Arbor to see the place where Henry Sewall had demonstrated that pigeons could be immunized to the venom of rattlesnakes (4), because that work had pointed out the way to the discovery of diphtheria antitoxin.

In 1887, Dr. Sewall married Miss Isabel Josephine Vickers of Toronto, Canada, who survives him. In 1888, he received an honorary M.D. from the University of Michigan. During the winter of 1889, Dr. Sewall became first resident physician at the Adirondack Cottage Sanitarium under the founder, Dr. E. L. Trudeau, where Dr. and Mrs. Sewall occupied one of the first little one-room cottages (5). In 1890, he took up his permanent residence in Denver, Colorado, after having received an M.D. degree in 1889 from the University of Denver, and was invited to become Professor of Physiology in the Denver and Gross College of Medicine, fulfilling this capably from 1890 to 1908. In 1912, the University of Michigan conferred the Sc.D. degree, and Wesleyan in 1926. In 1911–1918, Dr. Sewall occupied the chair of Professor of Medicine at the University of Colorado School of Medicine and was Emeritus Professor from 1920 on (6). His interest in public health asserted itself as Assistant Health Commissioner of Denver, 1891–1893, and Secretary of the Colorado State Board of Health from 1893 to 1899. He served the National Board of Medical Examiners during the trying early period of its inception in 1915 to 1919. His profound interest in climatology

led to his election to the Presidency of the American Climatological Association in 1914. In 1916, he was President of the Denver City and County Medical Society and in 1915–1916 of the American Association of Physicians. In 1924, the physicians of Colorado honored him by election to the Presidency of the Colorado State Medical Society (7), and in 1926, he became President of the National Tuberculosis Association (8). With the inception of the AMERICAN REVIEW OF TUBERCULOSIS in 1917, Dr. Sewall became a member of the Editorial Staff, an appointment which he held to the time of his death, because of his profound interest in the welfare and success of this scientific medical publication, not to mention his admiration and affection for the Editor, Dr. Allen K. Krause. His sound advice, guidance, and willing coöperation were sought repeatedly by Dr. Krause, who valued highly Dr. Sewall's friendship and suggestions. In 1919, when the Research Department of the National Jewish Hospital at Denver, Colorado, was established, Dr. Sewall became a member of the local Research Advisory Board, a member of the National Research Advisory Board, as well as an active investigator in the Department. His conscientiousness and industry are attested by the numerous publications of fundamental investigations in tuberculosis emanating from his pen (9). Included among these were notable studies on pulmonary atelectasis in 1921 and 1930, limiting respiratory excursions in pulmonary tuberculosis in 1921, climate and tuberculosis mortality in 1923, vitiated air in tuberculosis in 1924 and 1927, spontaneous tuberculosis in guinea pigs in 1928, artificial pneumothorax in pulmonary tuberculosis and motility of the mediastinum in 1928, resistance as represented by X-rays in human pulmonary tuberculosis, and, finally, many years of observations on immunity and allergy in tuberculosis. Among a few of his notable general interests on which he contributed to the literature were *Private Practice and State Medicine*, *Hospital Heat*, *Visualizing Medical History*, and *The Sanatorium as a School in Tuberculosis*.

On the evening of Wednesday, May 7th, 1930, in a general meeting of the National Tuberculosis Association, Dr. Sewall was awarded the Trudeau Medal for his scientific investigations in tuberculosis. On the 6th of May, 1931, he was awarded the Kober Medal of the Association of American Physicians. At this time he also received a document from the Kober Foundation of the Georgetown University of Washington, D. C., "acknowledging his commanding knowledge of medicine." Professor Thomas McCrae in making the presentation said, "Perhaps

you will take it as proof, not that such is needed, of the excellence of the work which you have done in many different fields of medicine." On Thursday evening, December 3, 1931, the medical profession of Denver honored Dr. Sewall with a testimonial dinner, at which time they presented to the Medical Society of the City and County of Denver an unusually fine oil portrait of him, which was placed in the medical library. The portrait was painted by the talented artist, the late Mr. J. I. McClymont of Colorado Springs. Dr. Gerald B. Webb (10), who gave the principal address of the evening, on *Dr. Henry Sewall—A Tribute*, made special mention of Dr. Sewall's illustrious heritage. Thomas Sewall, his distinguished grandfather, was graduated at Harvard in 1812, taking the Boylston Medal. He had been a great experimentalist, establishing the absorption of substances through the skin and studying the effect of alcohol on the stomach. He delivered the opening address of the Columbian College Medical School in 1825, a school which is now part of the George Washington University. "At a time when anatomical and pathological studies were difficult the scientific zeal of Thomas Sewall unearthed the necessary material." The father of Henry Sewall was a clergyman and possessed a gift of language which also characterized the son. Webb in commenting on Sewall notes, "The original mind like Sewall's is rare, a mind which 'Finds tongues in trees, books in the running brooks, sermons in stones, and good in everything.' " In closing, he said, "If you will look around you tonight, Doctor Sewall, you will see your monument in the physicians you have inspired."

Dr. Henry Sewall's life was dynamic and purposeful. It is best portrayed by a paragraph taken from Gracian's (11) rare philosophy:

> A man at his best. You are not so born: strive daily to develop yourself in your person, in your calling, until perfection is attained: the fullness of your every gift, of your every faculty you will know it in the improvement of your taste, in the clarification of your thinking, in the maturity of your judgment, in the control of your will. Some never attain the perfect, something always being lacking, and others are late in coming to themselves. The man complete, wise in speech, wise in action, is admitted, yea, he is even welcomed into that rare fellowship of those who understand.

H. J. C.

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HENRY SEWALL

ALLEN K. KRAUSE

To reach ripe age has ranked among the chiefest of Life's blessings: and doubly blessed he who plods the purple slope but hardly touched by the infirmities of age.

If this is so, what shall we say of him whose faculties expand as Age descends; whose insight grows the sharper with each heaped-up year; whose fancy plays more lightly yet more true; whose mind reaches out the more; and whose zest shows out more keen—to feel the freshness of the mountain breeze, to thrill with the sparkle of the rushing tide aslant the glittering sun, to soar with the new idea set free by some daily observation and put to test by ingenious experiment.

For such was Henry Sewall: such the man at past four-score,—indeed, more vividly than words can paint. High and bald was the brow, and the beard and temples white. But the visage!—ever alight, in play with clear and even lustrous eye, skin pink and smooth and with scarcely a true wrinkle, and arresting mobility of feature lending point to every move and gesture.

There were some of us who envied the men who lived in Colorado:—Harry Corper, with work-room nearby; Gerald Webb, admiring and admirable disciple; James Waring, whose home was but at the end of the street—"fidus Achates," every one. Theirs the opportunity for a fascinating and stimulating hour at will; ours but the meagre distillation of the occasional meeting that might bring us in contact with Henry Sewall. Childless himself, he took to heart and watched over the affairs of his much younger intimates with a concern that seemed genuinely parental. Without the least glimmer of intrusion he could find the occasion to insinuate a counsel that few could match or give so well. The older he grew the greater seemed his delight in the company of his juniors; the more lively the give and take of ideas with them; the bolder, the more daring, the more soaring the play of his imagination. Yet there was no hint of straining to make a point—an impression. Here was a man (so it appeared), well past the allotted span, whose nature

unstudiedly responded more youthfully than any call that roused it;—who left indeed the impression—always—that an exchange of ideas had, in some unaccountable way, led his companion into more youthful modes of thought and points of view than the latter was accustomed to use.

Near the surface of this remarkable octogenarian lay an unquenchable curiosity that age could not dull. How much he himself appreciated this stands out in a self-revealing paper he wrote but three years before his death.[1] He is writing in the third person: "And so start," he says, "a long career to satisfy curiosity; to hunt the meaning of things and, above all, to find out the Why of common occurrences that people accept as self-explanatory. . . . And this was the only talent he had—a longing to make dumb things speak their meaning." There was nothing of the blasé in Henry Sewall. It took but little to release the spirit of inquiry, easily rising to enthusiasm, the more intense, if anything, as age advanced, and the envy of many a young associate.

Outstanding was a deep, all-pervading and ever-lively vein of fancy. This made him a gay man—one to match badinage with man or woman of whatever age; one also to upset the serious conversation that had begun to list too heavily or flag deadly. Here his range was wide:—from the hesitant, seemingly apologetic suggestion, as eyes narrowed and hand groped out as though searching for the apt—the precise—remark; to the resounding "haw—haw—haw," body arching forward and hand descending with mighty slap on knee, immediately to rebound outstretched with finger pointed at his listener. There was the chuckle—the chortle—the hearty laughter—the unrestrained guffaw: or, maybe, the look of blank amazement, features fixed, with eyes wide and staring and lips apart; or the face in puzzled pose,—brow wrinkled, eyes almost closed and mouth in slight tremulous movement, as though the man were trying to grasp the full meaning of the question at hand. But, whatever was to come with the relaxation of these so characteristic Sewallian expressions one could be sure of one thing:—the remark would be winged with fancy—a seemingly inevitable solemnity would resolve on a gay chord.

Surely, all was not whimsy; but, in the ordinary conversation, intercourse, communion, that men live by, Henry Sewall never turned or settled a point without a touch of the whimsical, the unexpected. In this his capacity was inexhaustible. And, of course, he who cannot take

[1] *Journal of the Outdoor Life*, 1932.

himself too seriously is always a loveable man. And this man did not use fancy to cloak intellectual fog or fuzziness. His was a fancy born of no capriciousness: it was the saving, the salty side of his make-up. With it he illuminated the dark crannies that can cloud human existence. He taught by parable: it was his way: it could not have been otherwise.

Henry Sewall's passage through his sixties and seventies was a magnificent lesson to us all—an illustration of the truth of Plato's dictum that "there is in old age great peace and freedom."

"Peace and freedom" for what? Surely not for the enjoyment of power, pelf or position:—not for this man. It is as certain as can be that these more vulgar "summa bona" of human endeavor never raised Henry Sewall's pulse a single beat. But "peace and freedom" to assemble his faculties and apply these,—now, when all too commonly spent,—to the precarious business of wringing a new answer or two from the limitless mysteries of natural phenomena—from the "common occurrences that people accept as self-explanatory." "Peace and freedom" to exercise, if ever so little, an insatiable inborn curiosity concerning the inner nature of "things" that lay close at hand and seemed plain enough to less inquiring minds:—here was the thing!

As he approaches "three score and ten," he writes in a letter (January 18, 1924):

> I still have to earn a living . . . Even though my output here [on a "holiday" in Florida] has been nil certain things that were dim have become clearer & I go back [to Denver] with the hope that I may have found a key to the code of 10 yrs. work. As Hamlet says, the Play's the Thing, and like a child hearing stories one's appetite is never cloyed with the infinite variety of theme and adventure.
>
> No doubt it is proof of a petty mind not to shiver in the shadow of the ultimate but I long since abandoned effort to reason on the scientifically unknowable; hence one can respect the faith of those who are lucky enough to have it.
>
> The good old tree of knowledge still has tasty fruit hanging from its lower twigs for one unskilled to climb. It has been my good luck to enjoy the quest, with no despair for failure.

It is again more than ten years later. The avid aging explorer of "the good old tree of knowledge" has all but finished his seventies and is entering the latter half of his eightieth year (October 18, 1934), when he pens another letter.

I am now moved . . . to dilate a bit on the adventures of my own in old age. If I survive next May I shall be in my 81st year—almost a shameful record in view of recent paternal ancestry & taking account of the fact that I was always considered up to 15 as the weakling of the flock—makes one think as if he had stolen something. . . .

. . . one must know the extremes of life to realize that life is a circle & extremes meet & that the little tot clinging to the mother's gown knows a love that may disappear for years & years & then bloom again—just as the flowers are doing now in our garden. . . . Apropos of old age: it is a worth while adventure; too bad that the inspirations that throng upon one in contemplating sunset perspectives cannot be brought to expression,—but one grows more & more inarticulate; at all events one finds that the physics of life is more & more permeated with feeling,—and temperament. In my nightly bed-reading I am getting more thrill than from anything else in the reading of a tiny volume of the Psalms of David! now laugh! . . . when I think of the opportunities they [the Jews] have given me for over 15 years & saved me from the hell of loneliness in old age—I call them the blessed race. . . .

I feel that parts of my cortex are better than ever & one looks now with regret at waning physical powers & then looks forward to endless peace.

The ten years between the above abstracted letters—his seventies—must have been among the happiest of Henry Sewall's life, as they were among the most productive, and certainly the most influential and satisfactory.

A work-bench and Henry Sewall made a laboratory just as surely as a log with Mark Hopkins at one end and a student at the other made a college: "he could be content with a bench or a room, so long as his colleagues were there for communion."[2] Modestly, he never ceased to thank the authorities of the National Jewish Hospital for facilities for self-occupation that helped to dispel that "hell of loneliness" all aging active men must dread. His published work between 1921 and his death comprised thirty-three articles, in number almost one-quarter of his total listed "Bibliography," and most of these based on experimental work at the National Jewish Hospital. Little by little, he dropped out of practice altogether, attuning his needs to a very modest income indeed, always the more intent so to "organize" his time and mode of life as to wring the last possible drop of the student's and discoverer's delights out of a term which, however uncertain it might be, must, as he realized, be all too short and relentlessly limited.

[2] Corper, H. J.: *Amer. Rev. Tuberc.*, 1937, *35*, 400.

He realized also what was making possible the successful enjoyment and fruition of his old age. Not the boon of an extraordinarily preserved mentality and general physique: even though he had been "the weakling of the flock" and his paternal ancestry had been "shot through" with pulmonary tuberculosis, to which he too had once bent the knee: and, though he gave every appearance of unusual physical vitality, he lived his last twelve years increasingly bothered and handicapped by the remains of a serious surgical operation.

Nor would his vanity (or lack of it) permit him to seek the explanation in exceptional innate powers of adaptability to circumstance—to the happy possession of the proper temperament or the exercise of a correct practical philosophy, to smooth successfully his waning years with their proverbial toll of mounting difficulty and distress.

No:—he never doubted why he was succeeding where few men do. On the contrary, he never failed to formulate the answer, or to touch upon it, often in introducing a letter. In one letter he is quite explicit:

> There is one obvious and satisfactory explanation—showing the importance of selection in the chance vicissitudes of environment. My explanation is in the wife who became mine at early middle age just when tuberculosis had marked me for a victim and I followed the cowardly rule of such subjects and sought a vine to bear me up . . . it has been a more and more blessed experience.

And it was in the "homey" retreat on Vine Street, created by the "vine to bear me up," and arranged with every detail that would minister to the everlasting student's dream—"to find out the Why of common occurrences that people accept as self-explanatory,"—that the end came one morning last July,—unexpectedly, yet as Henry Sewall would have wished it. And, too, in full character: for, to quote the Denver *Rocky Mountain News*, "he reached for tablet and pencil at the bedside. With faltering fingers he wrote down the time and his temperature and noted that his skin was moist. Then he died."

THORACOPLASTY WITH LUNG MOBILIZATION

Part I. The First-Stage Operation

RICHARD H. OVERHOLT[1]

The operation of thoracoplasty has come to be the most valuable of all permanent collapse procedures in the treatment of pulmonary tuberculosis. Since the operation is followed by a permanent and irreversible alteration of the thoracic wall, a certain ideal of perfection in the plan and execution of the thoracoplasty in each individual is necessary. The objective should include the following points: first, a complete collapse of totally diseased lung; second, a conservation of uninvolved pulmonary

ERRATUM

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On page 347, in the title of the article by Lewis J. Moorman the word *Contracts* should be *Contacts*.

patient.

A great step toward the selective and conservative goal was taken when the upper multiple-stage limited thoracoplasty replaced the complete paravertebral thoracoplasty. Another advance, and possibly as equally an important one toward the ideal thoracoplasty, is now being taken. This step is the addition of a supplementary procedure, lung mobilization, to the usual upper-stage rib-resection. An extrafascial separation of the apex of the pleura (extrafascial apicolysis) can be carried out at the time of the first-stage thoracoplasty, and further mobilization of the lung can be done at the second-stage operation. The principles underlying this additional procedure are sound. The degree of collapse more nearly simulates the perfect selective collapse of pneumothorax than

[1] Division of Thoracic Surgery, Lahey Clinic, Boston, Massachusetts.

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A great step toward the selective and conservative goal was taken when the upper multiple-stage limited thoracoplasty replaced the complete paravertebral thoracoplasty. Another advance, and possibly as equally an important one toward the ideal thoracoplasty, is now being taken. This step is the addition of a supplementary procedure, lung mobilization, to the usual upper-stage rib-resection. An extrafascial separation of the apex of the pleura (extrafascial apicolysis) can be carried out at the time of the first-stage thoracoplasty, and further mobilization of the lung can be done at the second-stage operation. The principles underlying this additional procedure are sound. The degree of collapse more nearly simulates the perfect selective collapse of pneumothorax than

[1] Division of Thoracic Surgery, Lahey Clinic, Boston, Massachusetts.

any permanent procedure yet proposed. (See figure 12.) The direction of the collapse is downward and forward, as well as medialward. The operation is technically possible and can be done safely.

The results of combining lung mobilization with upper thoracoplasty so far indicate that the patient is benefited in several ways:

1: A more effective collapse of the upper lobe is obtained, obviously of importance in treating large apical cavities.
2: The clinical improvement shown by the patient following the first stage is more striking.
3: The first stage of the operation leaves all uncollapsed lung below the level of the unresected ribs. It is therefore possible to lengthen the interval between stages without jeopardizing an effective final collapse.
4: Supplementary operations have been less frequently employed. This applies to anterolateral and parasternal thoracoplasties as well as to revision operations. The use of the combination of lung mobilization and thoracoplasty has resulted in a slight reduction in the average number of stages for the patient.

This report is based upon a comparative experience with 253 patients, upon whom 573 thoracoplasty procedures have been carried out. In 147 patients lung mobilization was not carried out at the time of thoracoplasty. The majority of these patients were treated between June, 1932, and February, 1935. Since the later date and June 1, 1936, 106 patients have been treated by the combined operation of thoracoplasty and lung mobilization. Year by year more serious risks are accepted for thoracoplasty when other methods fail to check the progress of the disease. In the former group (thoracoplasty without lung mobilization) only 15 per cent had active bilateral disease at the time the operation was carried out. The operative mortality was 6.4 per cent. In the later group (thoracoplasty with lung mobilization) 28 per cent of the patients had bilateral active disease with cavitation, yet the operative mortality was 5.6 per cent.[2] It has been our experience, therefore, that the addition of lung mobilization to the thoracoplasty has not increased the risk of the operation.

Recently, a survey was made of all living cases in these two groups as to the effectiveness of the operation. In the first group (thoracoplasty without mobilization) the collapse was considered satisfactory in 95 of

[2] These figures include all cases operated upon, regardless of complications, such as amyloid disease, tuberculous empyema, bronchopleural fistulae, etc.

the 133 patients, 71 per cent. In the second group (thoracoplasty with mobilization), the collapse was satisfactory in 86 of 93 patients, 92 per cent.

A survey has also been made in regard to the frequency of contralateral extension or spread during the course of the operative procedures. In the first group, an extension was noted in the contralateral lung in 11 patients. In the second group, an extension was demonstrated in 7 patients. Therefore, fear of increasing the likelihood of a dissemination of the disease should not be used as an argument against lung mobilization at the time of thoracoplasty. It is also true to say that we have observed an extension or a spread of the disease in several times this many patients who refused thoracoplasty or had their operation delayed from one cause or another.

In view of the fact that all operations in both groups were done within a four-year period and the second group within the past eighteen months, an analysis of end-results cannot be made. A detailed follow-up study is in progress and a report will be given subsequently.

The value of extrafascial apicolysis as an adjunct to upper thoracoplasty has been described by Semb (1). In a very comprehensive paper, he pointed out the anatomical structures which suspend the apex of the lung, the manner in which they prevent a vertical collapse of the lung, and the technique of the mobilization of the lung, as well as the necessity for doing the apicolysis extrafascially.

There were two conditions which aroused our interest in the combined apicolysis and thoracoplasty operation. The first point was that the closing of large apical cavities was still uncertain, and, in addition, a few cases considered as ideal ones for thoracoplasty failed to close by what was apparently a satisfactory operation. From the fall of 1932 to February, 1935, our practice had been to do a complete removal of the upper ribs from the vertebrae (including the transverse processes) to the sternum. In reviewing the thoracoplasty failures, even though the collapse was apparently adequate, overexposed roentgenograms revealed a tongue of lung lateral to the vertebral bodies and extending as high as the first or second dorsal vertebrae. Within this tongue of lung the presence of a residual, slit-like cavity could be demonstrated. (See figure 11.) At the time of reoperation, after the regenerated ribs and chest-wall had been removed, the underlying lung was found to extend up to the brachial plexus and axillary vessels, and the extreme apex of the lung had remained at its preoperative level opposite the transverse process of the

7th cervical vertebra. The previous thoracoplasty had resulted in only a lateral collapse of the lung, failing to close the cavity. In the case shown in figure 11a, two revisions, in which regenerated ribs alone were removed, resulted in a failure to close the cavity. After a third revision, at which time the suspensory ligaments of the apex were divided and the upper lobe mobilized in the vertebral gutter as far down as the hilum, the lung became completely collapsed and the cavity closed. (See figure 11b.) We found it necessary to carry out extensive revisions in 20 of the patients who had not previously had the apical mobilization. The operation is difficult and carries a higher operative risk, and the results are uncertain. Three patients of the twenty died following the revision. In the second group, who had the mobilization, a revision has been necessary in only one patient to date.

The second point which interested us in combining extrafascial lung mobilization with thoracoplasty developed from an impression obtained in following the course of patients who had had an extrapleural plombage and who subsequently had the paraffin removed at the time the thoracoplasty was performed. When plombage preceded thoracoplasty, we seemed to have less difficulty in closing large apical cavities. The vertical collapse of the lung resulting from the plombage, together with the lateral collapse of the thoracoplasty, appeared to produce a more complete collapse of the upper lobe than we obtained with thoracoplasty alone.

With these results in mind and with a determination to eliminate the necessity for thoracoplasty revision, we began to develop a technique for combining lung mobilization with thoracoplasty in the winter of 1935. In the beginning the procedure was carried out only in the better-risk patients with large thick-walled cavities,—the group notably most difficult to successfully collapse by thoracoplasty alone. We soon found that the added 10 to 15 minutes necessary to carry out the lung mobilization was well tolerated on the operating table, and that the postoperative course was as free of complications as in the simple thoracoplasty cases. It was not long before the combined operation was adopted as a routine, and during the past eighteen months we have preferred it to the usual thoracoplasty procedure in all cases in which the upper lobe is involved.

Since the adoption of this technique, in only two patients have we considered it unwise to continue with the mobilization of the lung at the time of thoracoplasty because of the poor general condition of the patient or because of the operative course. We have come to believe that, the

poorer the risk, the more in need they are of the additional collapse provided by the freeing of the apex of the lung. Therefore, in the bad-risk case, we are very desirous of adding this procedure to the thoracoplasty. We are also convinced that it is important to carry out the mobilization in all those patients who have bilateral apical tuberculosis. An adequate collapse can be obtained with the removal of fewer ribs than without the extrafascial mobilization of the lung. In other words, the more extensive the bilateral pulmonary tuberculosis, the more imperative it is to conserve normal lung.

ANATOMICAL CONSIDERATIONS

It is well to review at this point the anatomical structures which suspend the apex of the lung. Both the Gray and Cunningham *Anatomies* acknowledge that the apex of the pleura is strengthened and held in place by an aponeurotic expansion, first described by Sibson, which is attached to the inner border of the first rib and behind to the anterior border of the transverse process of the 7th cervical vertebra. A most complete description of the supporting structures of the pleural apex can be found in the French *Anatomy* of Rouviere (2). In addition to the extension of the pleural fascial aponeurosis (Sibson's fascia or the endothoracic fascia) three ligaments or bands are described. These bands (Sebileau's bands) have been identified repeatedly in our dissections at operation. Sebileau's bands are as follows:

1: The costopleural ligament attaches the endothoracic fascia at the apex of the lung to the 1st rib posteriorly and is a well-defined, heavy band. This band passes posteriorly to the 1st dorsal nerve as the nerve crosses the internal border of the 1st rib to partake in the formation of the medial cord of the brachial plexus.

2: The vertebropleural ligament is a second supporting structure of the endothoracic fascia at the apex of the lung. This ligament orginates in the prevertebral aponeurosis and is lost in the superior internal portion of the endothoracic fascia. This band lies anteriorly to the 1st dorsal nerve. These two bands are in most cases well defined and require sharp dissection in separating them from the endothoracic fascia.

3: The scalenus minimus muscle is present in approximately one-half of individuals. It is a small muscle band taking origin from the transverse process of the 7th cervical vertebra, descending obliquely and tangentially to the apex of the endothoracic fascia, to which it attaches by numerous tendofascial bands, to end along the internal border of the 1st rib and outside of the insertion of the scalenus anticus muscle. In the other half of individuals

Fig. 1. Drawing illustrating structures which suspend the apex of the lung (after Rouviere). In addition to Sibson's fascia which is a continuation of the endothoracic fascia, there are three important bands (Sebileau's), which suspend the pleural dome independent of the support given by the 1st rib.

1. The costopleural ligament extends from the inferior surface of the posterior aspect of the 1st rib anteriorly to the 1st dorsal nerve to attach to the apex of the pleura. It descends anteriorly to the first dorsal nerve.

2. The vertebrocostal ligament arises from the prevertebral aponeurosis and is lost in the superior and internal portion of the pleural dome.

3. The vertebropleurocostal ligament extends from the transverse process of the 7th cervical vertebra to the pleural dome and to the internal border of the 1st rib. In many cases this ligament contains muscle fibres and is then called the scalenus minimus muscle. (Zuckerhand.) Note how firmly the pleural dome is anchored to the prevertebral fascia and to the transverse process of the seventh cervical vertebra.

(Zuckerhand) this muscle is not present and is replaced by a delicate fascial band,—the vertebro-pleuro-costal ligament. In our experience these fibres are not well defined and separate easily by blunt dissection.

In figure 1 is shown a drawing which illustrates the position of these three supporting structures and their relation to the 1st rib and the

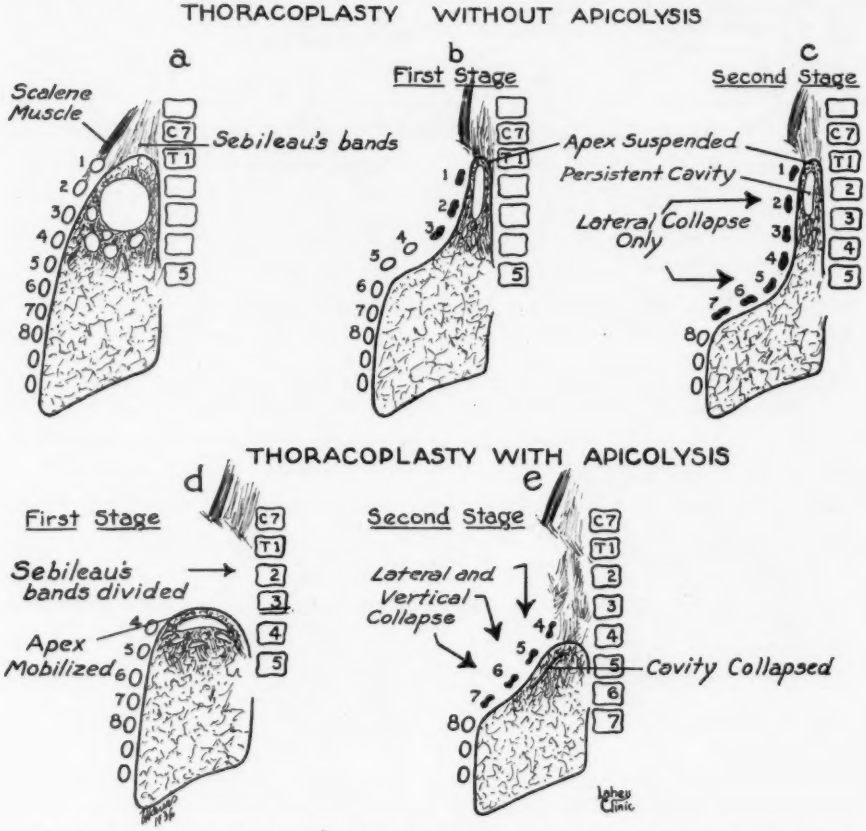

Fig. 2. Diagram illustrating the differences in the principle of thoracoplasty without and with mobilization of the lung. The resection of the ribs alone produces lateral collapse only. The position of the apex of the pleura remains unchanged. a. Preoperative position of the lung. b. After removal of three ribs. c. After completion of seven-rib thoracoplasty. Following the division of Sebileau's bands and "wiping down" of the apex extrafascially, the lung is collapsed vertically as well as laterally. d. After first stage. e. After second stage. Note that the periosteum of the 4th to 7th ribs was not disturbed and regenerated ribs have formed which aid in preventing a reëxpansion of the upper lobe.

scalene muscles. It is to be noted that the last two mentioned structures originate above the 1st rib, and that a removal of this rib alone, therefore, does not change the vertical position of the apex of the lung. Moreover,

the removal of the 1st rib and transverse process loosens the attachment of the costopleural ligament, and it is left attached to the periosteum of the 1st rib, which is in turn left attached to the vertebral bodies. In order to permit a descent of the apex of the lung, all of these bands and

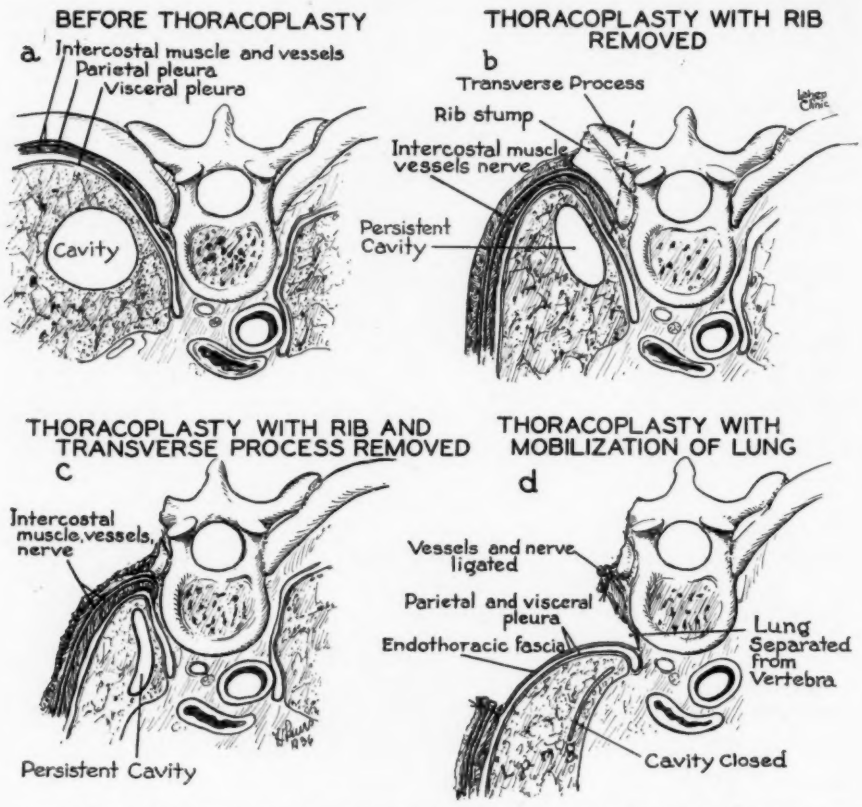

Fig. 3. Drawing illustrating importance of the posterior mobilization of the lung. a. Preoperative relationship of the lung to the posterior portion of the rib, intercostal vessels, nerve and periosteum of the rib. b. Effect of resection of rib only. Projecting transverse process together with vessels and nerve hold out the lung and prevent cavity closure. c. Effect of removing rib and transverse process. Note that posterior portion of the lung is still not adequately collapsed, due to the anchorage given by the intercostal nerve and vessels together with the periosteum of the resected rib. d. The posterior portion of the lung has been mobilized by a division of the anchoring structures. An obliteration of the vertebral gutter is then accomplished.

fascial fibres must be divided and the endothoracic fascia and pleura wiped down from the brachial plexus, the vertebral bodies, and anterior mediastinum. (See figures 2 and 9.)

A second anatomical point to consider in the mobilization of the upper

lobe is the posterior anchorage of the lung to the vertebrae by the intercostal vessels, nerves, and posterior periosteum. After the ribs and transverse processes have been removed, these structures strongly hold the posterior portion of the extrapleural fascia, parieta pleura, and lung posteriorly, and prevent a collapse of the lung in the vertebral gutter. In figure 3 a cross-sectional drawing indicates the way these structures prevent a satisfactory mobilization of the lung even though the ribs and transverse processes have been removed. The last drawing of figure 3 illustrates the manner in which a division of these structures and a mobilization of the posterior lung border from the bodies of the vertebrae results in a more satisfactory collapse of the underlying lung.

It is evident, therefore, that the suspension of the apex of the lung by strong fascial attachments and by Sebileau's bands, together with the posterior anchorage of the intercostal vessels, nerves and posterior periosteum prevents anything more than a lateral collapse of the upper lobe by a removal of the ribs and transverse processes alone. The mobilization of the lung, along with the extrapleural or endothoracic fascia with the attached periosteum of the resected ribs, removes all the supporting structures of the *cupola pleurae*. The severance of attachments of the endothoracic fascia and the periosteum and their mobilization together with the lung aid in the prevention of the reëxpansion of the apex of the lung. On opening the wound for the second-stage thoracoplasty, we have always found the apex of the lung at the level to which the apicolysis was extended at the time of the first-stage thoracoplasty, provided a satisfactory mobilization was done at the time of the first stage operation. The basis for the combined thoracoplasty and extrafascial mobilization therefore becomes clear, and, from an anatomical standpoint, sound.

THE TECHNICAL STEPS IN THE FIRST-STAGE OPERATION

The usual posterior upper thoracoplasty incision is used in the mobilization of the scapula and the exposure of the upper thoracic cage. The serratus magnus muscle is divided at its point of origin on the ribs and the longissimus dorsi muscles are separated from the posterior angles of the ribs and retracted medially. (See figures 4 and 5.) The posterior half of the 3rd rib and all of the 2nd and 1st ribs are then resected together with the transverse processes of the 2nd and 3rd vertebrae. The usual thoracoplasty stops at this point. It is not considered necessary to always remove the 1st transverse process. (See

figure 6.) Our practice has been to resect the 3rd rib only to the mid-axillary line at the time of the first-stage operation. If all of the upper three ribs are removed over the anterior portion of the chest, the rigidity of the costal cage is so weakened that paradoxical breathing is very likely to occur in the early postoperative period. A discussion of the

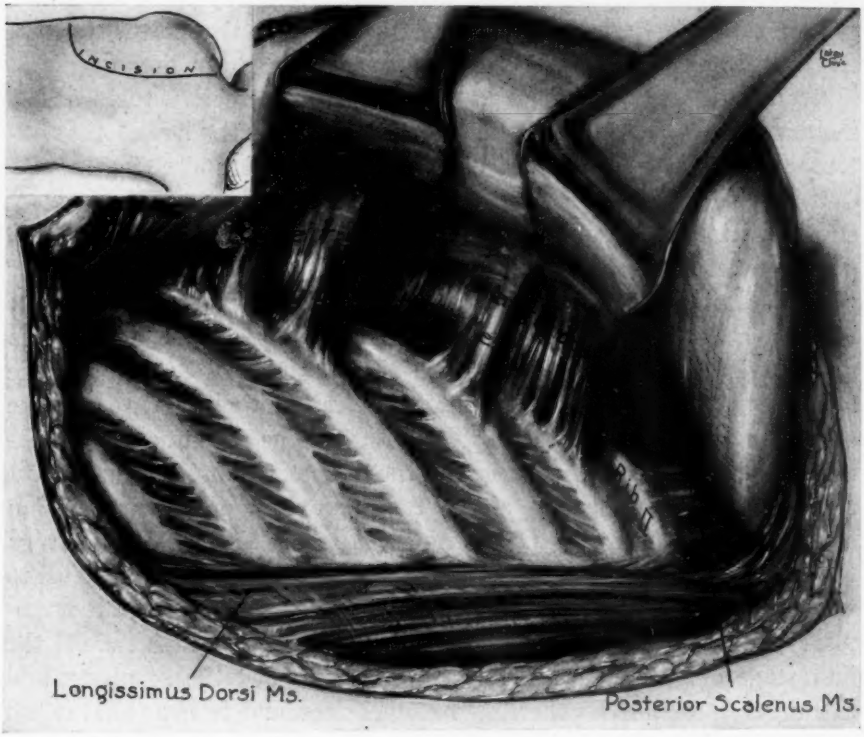

Fig. 4. Drawing illustrating the exposure necessary for the first-stage thoracoplasty. The incision should be carried from a high position on the back well below the scapula. This permits the incision of subsequent operations to be made wholly within the limits of the original scar down to the 7th or 8th rib.

treatment of the anterior portion of the third rib at the time of the second stage thoracoplasty appears in part II of this paper.

After the removal of the ribs and transverse processes of the vertebrae, the various steps in the mobilization of the lung are as follows:

1: Ligation and division of the 1st and 2nd intercostal vessels and nerves and the removal of the 1st and 2nd intercostal muscle bundles. The extreme posterior portion of the lung is then separated from the vertebral bodies. (See figure 7.)

2: The supporting structures (Sebileau's bands) are put under gentle traction with a gauze sponge beneath the hand on the lung. (See figure 8.) The bands are then easily divided with the dissecting scissors, the division being

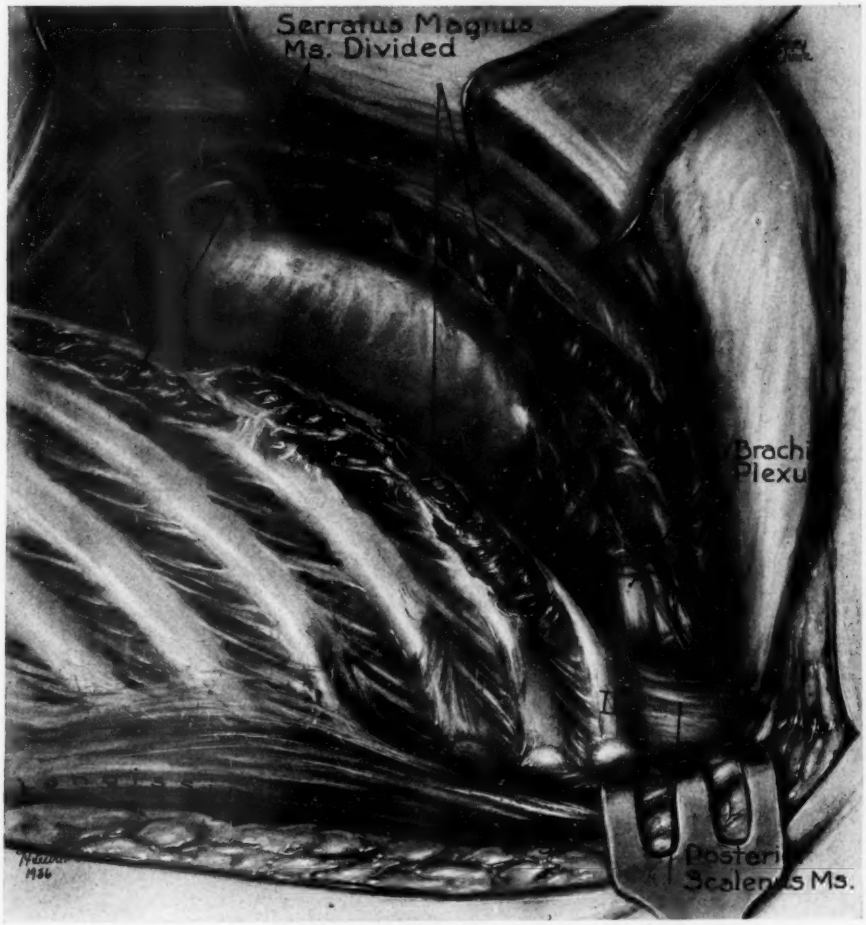

Fig. 5. Exposure of upper thoracic cage completed. The attachments of the serratus magnus muscle to the ribs are completely divided by sharp dissection. The periosteum of the ribs should not be separated with the muscle, since regenerated bone in the position of the retracted muscle would not be desirable. Note how adequately the 2nd rib, the posterior scalene muscle and brachial plexus are exposed.

started posteriorly. First, the costopleural ligament, which is posterior to the first thoracic nerve, is divided, and then the pleurovertebral ligament, and last, the vertebropleurocostal ligament. The brachial plexus and subclavian vessels come into full view. Injury to these structures is avoided by

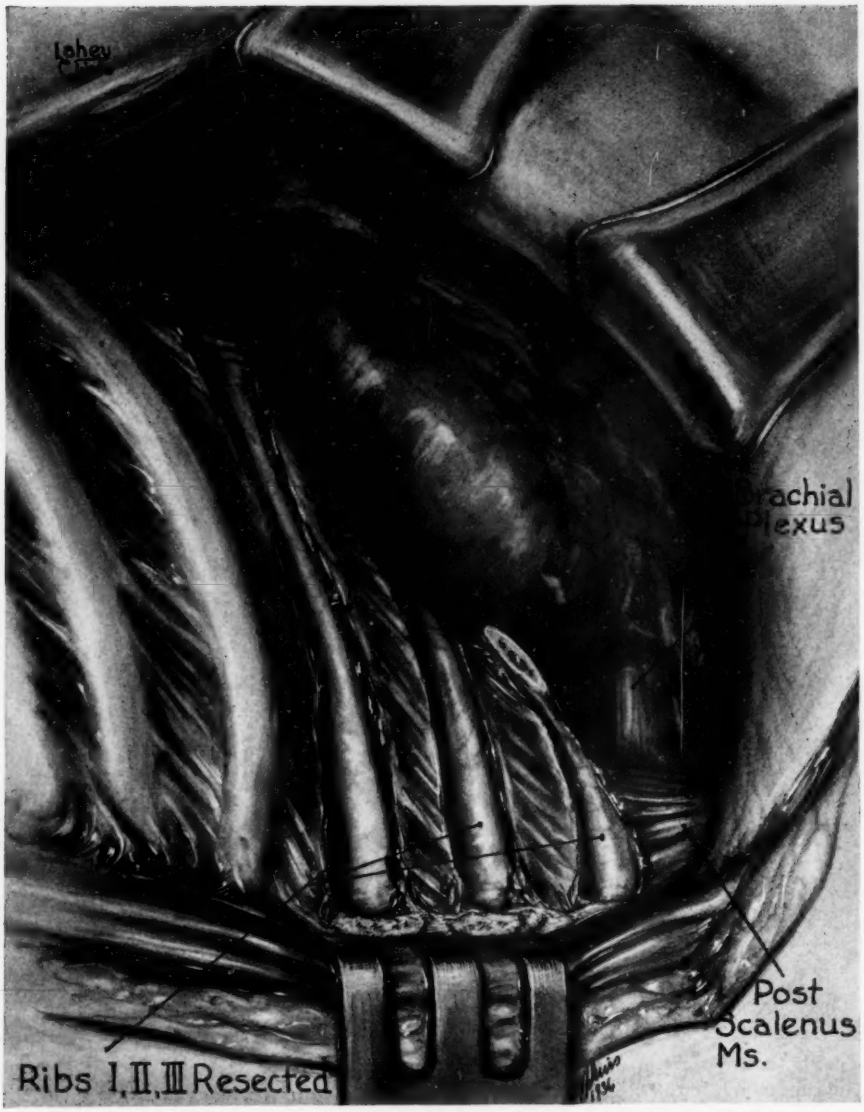

Fig. 6. Completion of the rib-resection of the first stage. All of the 1st and 2nd ribs and the posterior half of the 3rd rib have been removed, together with the transverse processes. In the past, most upper thoracoplasty procedures were concluded at this point. The apex is still suspended and lateral collapse only is provided.

careful dissection and wide exposure. A small piece of gauze in a curved haemostat is used to wipe the extreme apical pleura reflexion from the brachial plexus and subclavian vessels. The pleural reflexion is then separated from

the anterior mediastinum by blunt dissection. The mobilization is usually carried down to the level of the 4th rib.

The large mediastinal vessels, visible when operating on the right side, are the right innominate vein, the superior vena cava, and at times the superior intercostal vein, rarely the vena azygos as it arches forward to

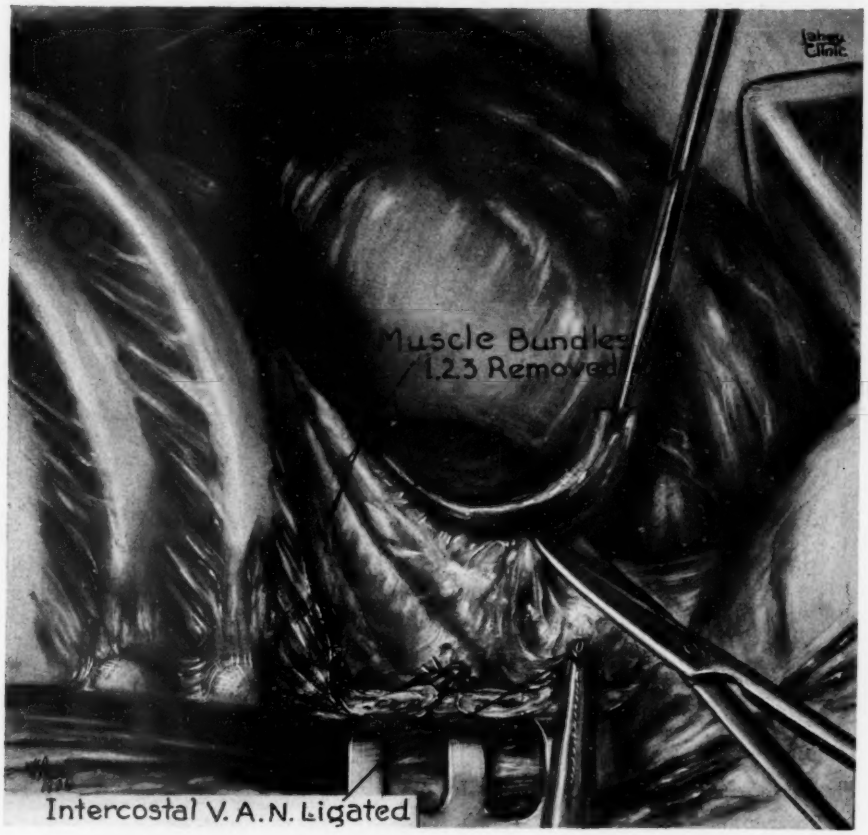

Fig. 7. The first step in the mobilization of the apex. The vessels, nerves, muscles and periosteum of the 1st and 2nd ribs are removed.

join the superior vena cava. On the left side the mediastinal vessels visible are the left innominate vein just after the junction of the left subclavian vein and the left internal jugular vein, the subclavian artery, the arch of the aorta, and at times the superior intercostal vein.

The anterior ends of the 1st and 2nd ribs are easily resected at the sternum after the completion of the apicolysis. The 3rd intercostal

nerve and vessels are usually left intact, but may be resected. At the conclusion of the apicolysis the position of the apex of the lung is at the

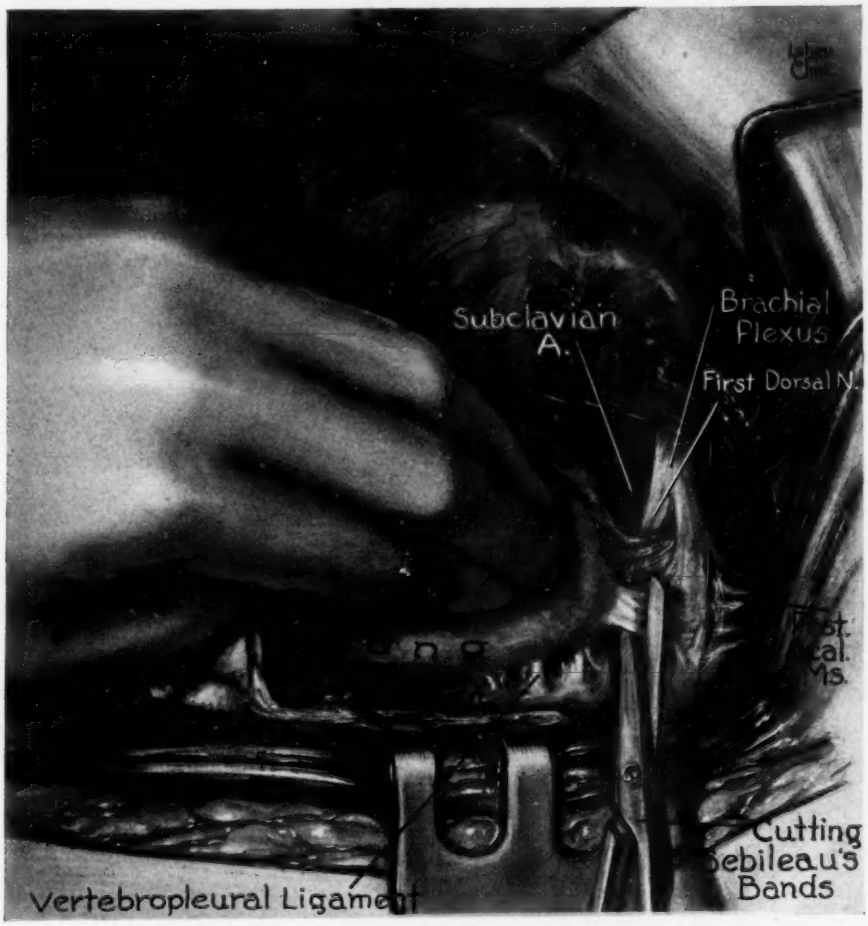

Fig. 8. The endothoracic fascia over the lateral surface of the lung is exposed. Sebileau's bands then come into view, and can be divided by sharp dissection. The costopleural ligament is the first band to be encountered. Note the posterior attachment of the endothoracic fascia to the vertebrae. The brachial plexus comes into full view, and the subclavian artery and vein are isolated.

level of the 4th rib. The lung is covered by the pleura and endothoracic fascia. (See figure 9.)

Emphasis should be placed on the fact that the mobilization of the apex of the lung is accomplished by the division of the supporting

Fig. 9. Completion of the mobilization of the apex of the lung. The separation was carried out extrafascially. The pleural dome now lies on a level with the 4th thoracic vertebra. The separation of the pleura anteriorly should include a separation from the anterior mediastinum as far down as necessary to close the underlying cavity. It is possible to wipe down the pleura on the mediastinal surface as far as the hilum of the lung.

structures to the endothoracic fascia, so that what remains of the chest-wall itself is carried down with the lung. In the operation of plombage the dissection is carried out between the parietal pleura and the endothoracic fascia and leaves the supporting structures intact. The space,

however, is filled with muscle, paraffin, or some other substance which prevents the reëxpansion and reëlevation of the apex of the lung. If such an apicolysis were performed at the time of thoracoplasty, that is, separation of the parietal pleura and endothoracic fascia without the division of apical bands and vertebral attachments, there would be nothing to prevent a gradual reëxpansion of the apex of the lung to its original position. After an extrafascial apicolysis, the lung is found at

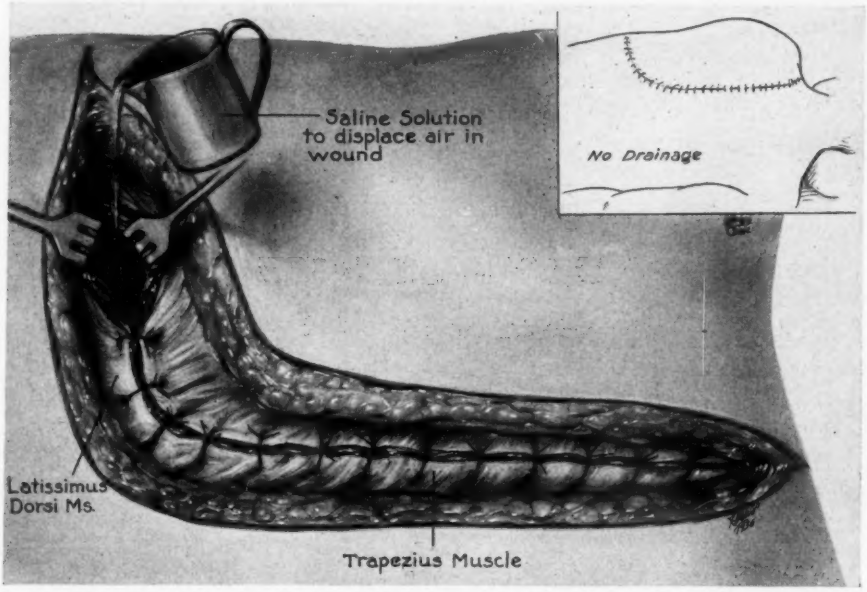

Fig. 10. Wound closure. Interrupted sutures are used in the muscles and skin. A sufficient amount of saline solution is poured into the wound to displace all air in the space above the lung and beneath the scapula. This eliminates the possibility of emphysema of the tissues and prevents a reëxpansion of the lung before thickening of the tissues anchors it permanently in its new position.

the level of the 4th rib when the wound is opened for the second-stage thoracoplasty. The regeneration of osseous tissue from fragments of the periosteum of the resected ribs and the formation of scar-tissue in the region of the apicolysis prevent a reëxpansion of the lung.

The wound is closed by replacing the scapula and approximating the muscles with interrupted catgut sutures. Before all of the sutures are placed in the lower angle of the wound, a sufficient amount of physiological saline solution is poured into the wound to displace all of the air in the space beneath the scapula. (See figure 10.) Replacement of the

air by fluid accomplishes two things: (1) emphysema of the tissues of the mediastinum and cervical region is eliminated and (2) greater stability of the mobilized lung is accomplished. The saline solution is gradually replaced by serum which may not be absorbed for six to eight weeks and even longer. The stabilization of the apex of the lung by fluid is de-

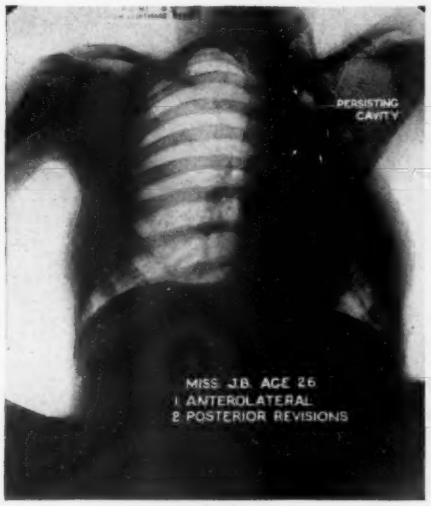

Fig. 11a

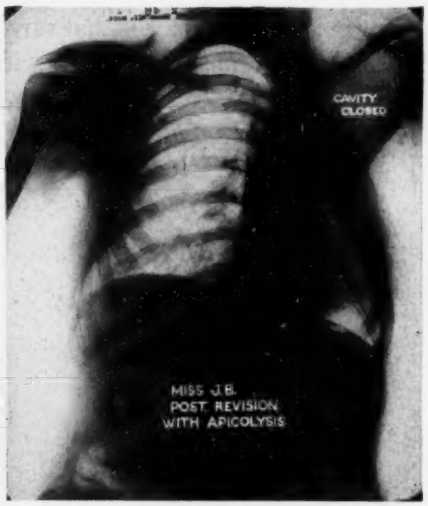

Fig. 11b

Fig. 11a. Postoperative roentgenogram in the case of Miss J. B., showing result of an extensive thoracoplasty without lung mobilization in which a persisting cavity can be seen in the vertebral gutter. The first series of operations consisted in a three-stage posterior thoracoplasty, including transverse processes, and then later a parasternal resection of anterior rib segments and cartilages. On two separate occasions, a posterior revision was done at which time regenerated ribs were removed. All of these procedures failed to close the cavity. Note how close the transverse processes were trimmed and how apparently satisfactory the thoracoplasty seemed to be from an anatomical standpoint.

Fig. 11b. Postoperative roentgenogram in same patient, Miss J. B., after a posterior revision with mobilization of the lung was done. After the removal of a portion of the reformed chest-wall, the upper lobe was completely mobilized, all apical and vertebral attachments were divided extrafascially, and the lung was permitted to retract toward the hilum. Following this procedure, the cavity closed, coughing ceased, and the sputum has been consistently bacilli-free when examined after concentration.

sirable to prevent trauma of the lung by coughing in the early post-operative period. The fluid also keeps the apex of the lung collapsed until the tissues have sufficiently thickened to hold the lung in its new position.

After the wound has been filled with saline solution, it is closed without drainage. Fine interrupted silk ligatures are used for the skin closure.

ANAESTHESIA

During the past two and one-half years, cyclopropane general anaesthesia has been used for all thoracoplasty operations upon tuberculous subjects. The anaesthesia question is mentioned here because we consider it one of the important factors which contribute to the safety of the operation. Cyclopropane as an anaesthetic agent has one overwhelming point in its favor, which is that surgical anaesthesia can be produced with low concentrations of the gas itself which permits the simultaneous ad-

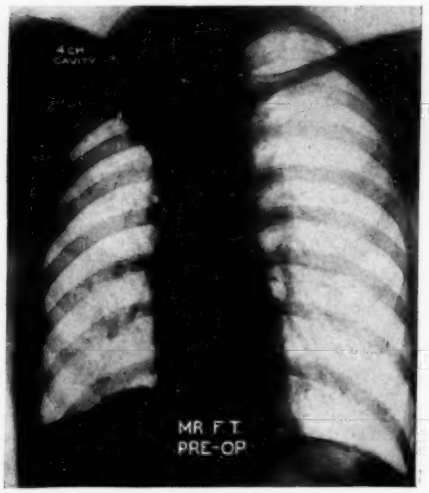

Fig. 12a

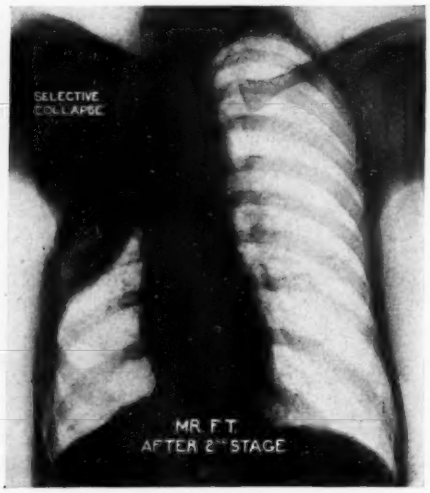

Fig. 12b

Fig. 12a. Preoperative roentgenogram in the case of Mr. F. T., age 42. Note large apical thick-walled cavity.

Fig. 12b. After selective thoracoplasty and mobilization of upper lobe. Operation done in two stages with six weeks' interval between stages. Note effectiveness of collapse and conservation of healthy lung. Also note the relatively small amount of scoliosis.

ministration of large quantities of oxygen. Induction is rapid, breathing is slow, respiratory excursions are of small amplitude, and the blood is well oxygenated. Recovery from the anaesthesia is rapid, so that the cough reflex is not interfered with during the early postoperative period.

Quiet, controlled respirations are absolutely essential in the safe performance of apicolysis with thoracoplasty. Irregular, labored, or forced respirations, and especially coughing, might result in a rupture of the lung if it occurred while the apex was exposed and the scapula elevated. On one occasion during the course of extrapleural apicolysis,

done for the purpose of inserting paraffin under local anaesthesia, the patient coughed and blew a hole in the unsupported apex of the lung. Ideal anaesthetic conditions should exist before apicolysis is attempted.

Our experience with the combined apicolysis and thoracoplasty has so convinced us of its value that we feel every effort should be made to provide the type of anaesthesia which permits the surgeon to add this procedure to his armamentarium.

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THORACOPLASTY WITH LUNG MOBILIZATION

Part II. The Second- and Subsequent-Stage Operations

RICHARD H. OVERHOLT[1]

The ideal procedure in the permanent alteration of the thoracic wall for pulmonary tuberculosis calls for selectivity in the collapse of the lung in the diseased area, conservation of healthy lung, and a plan of execution of the operation that provides the greatest factor of safety for the patient. The indications for the extent and the intervals of subsequent operations are being treated separately to emphasize the necessity for planning subsequent stages as individual operations.

In the early thoracoplasties the lower ribs were resected first, the upper ribs being resected at subsequent operations. A complete collapse in the region of the first operation was prevented by the overarching upper ribs in the interval between the first and subsequent operations. A delay in the resection of the upper ribs resulted in a poor collapse due to the regeneration of the previously resected ribs. In other words, a long interval was not desirable because of stiffening of the tissues before all ribs were resected. Thoracic surgeons became so convinced of the necessity for a rapid sequence of operative stages that even to-day we find it is considered necessary by the majority of men doing surgical tuberculosis work.

Our experience has convinced us that the planning and execution of multiple-stage thoracoplasties with short time intervals is not the safest for the patient nor the most conservative of healthy lung. Selecting the most favorable time for the second operation demands a delay sufficient for the patient to recover fully and receive all of the benefits that will follow the collapse provided by the first operation. A delay is also necessary to determine whether an additional collapse is required and of what extent.

Thickening of the tissues and stiffening of the thoracic wall will occur in 10 to 20 days following operation. This period of time is insufficient for the patient to have regained his appetite and strength, and to have

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made up for the blood lost at the time of operation. Certainly, the patient is not in good condition for a second major operation in 10 to 20 days. Following the teaching of rapid successive operations, we found that in some cases the stormiest convalescent period occurred after the second or third operation. Some of the earlier postoperative deaths took place after the second- or third-stage operation in cases that were apparently good risks. There is no way to predict the manner in which any given case will react to two or three major surgical operations if subjected to them within a short period of time.

The studies of Overholt and Pilcher (1) on venous-pressure alterations after thoracoplasty demonstrated that when an elevated postoperative venous pressure occurred following the first stage, the return to normal was slow. McIntosh (2) has shown a reduction in the lung volume and vital capacity following thoracoplasty. Overholt and Harter (3) have also found a reduced lung volume and vital capacity following each stage of a thoracoplasty. Measurements of these functions at later periods show a progressive tendency to return to the preoperative values.

The second important reason for delaying the subsequent operation is equally as valid. The maximum benefits provided by the first operation develop after a lapse of several weeks. A lessening in the cough and in the amount of expectoration usually occurs. The condition of the lung on the operated side improves, and contralateral lesions, if present, are usually influenced for the better. In febrile cases often the temperature subsides and becomes normal under the influence of the apical collapse provided by the first stage thoracoplasty. The patient should not be subjected to a second major operation until the height of the recovery curve has been reached.

The third argument favoring a delay in thoracoplasty stages is concerned with the extent of subsequent stage procedures. In many cases the estimation of just how much the first operation has accomplished and what additional collapse is required is not easy in the first two weeks postoperatively. The roentgenogram is the most accurate guide. A postoperative lung reaction and a deep collection of serum in the wound obscures the fine detail of the lung during the first few weeks. (See figures 1, 2 & 3.) Usually a decision regarding the extent of subsequent operations should be deferred until such time as a clear roentgenogram may be obtained, unless there is an extensive unilateral disease and it is obvious from the start that two or more stages are necessary.

A prediction cannot always be made from the size of the cavity as to

the extent of the pulmonary collapse required. In bilateral cases it is extremely important to know exactly the extent of the collapse needed in each side and not to exceed that amount. If we adhere to the outline of the ideal thoracoplasty, as suggested in part I of this series of papers, and provide a selective collapse of the diseased area with as much conservation of healthy lung as possible, we must wait until the necessity for and the extent of subsequent permanent procedures can be accurately determined.

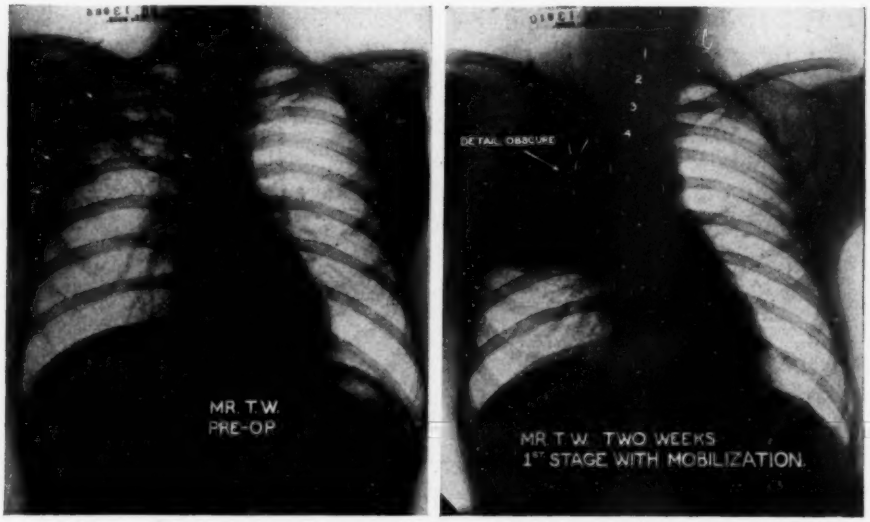

Fig. 1a Fig. 1b

Fig. 1a. Preoperative roentgenogram in the case of Mr. T. W. Note infiltration and small cavities in right upper lobe.

Fig. 1b. Roentgenogram two weeks after first-stage thoracoplasty and lung mobilization. Note that lung detail is obscured at this time. The second operation should be delayed until the roentgenogram may serve as a guide as to the extent of further surgery.

If the second- or subsequent-stage thoracoplasty is a delayed procedure, it follows, therefore, that each operation be planned so that it is relatively complete within itself as far as the collapse of the lung in that region is concerned. The first stage should not be too dependent for its success upon the next operation. Overholt (4) has pointed out that the above-down sequence of rib removal has permitted a much longer interval than the below-up thoracoplasty. However, the combined mobilization of the lung with the first stage, as described in part I, makes it still safer to delay subsequent stages for several weeks without jeopardizing

the final effect of the pulmonary collapse. (See figure 2.) At the conclusion of the operation, as pointed out in part I, the apex of the lung is left on a level with, or below, the rib to be taken out at the next stage.

The same criteria apply to the second-stage thoracoplasty as to the first stage in planning the length and number of ribs to be removed. Residual cavities should be closed and healthy lung conserved. A third-stage thoracoplasty should be planned if more than a safe number of ribs need to be resected to close the pulmonary cavities present at the time of the second-stage operation. A resection of four ribs is considered

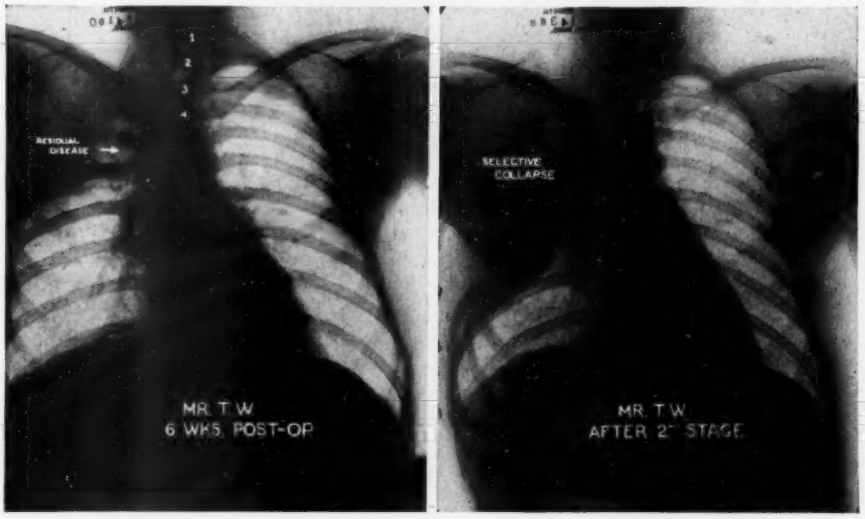

Fig. 2a Fig. 2b

Fig. 2a. Postoperative roentgenogram. Same case as fig. 1 (Mr. T. W.) six weeks later. Note clearing of lung field and extent of residual disease which is now clearly shown.

Fig. 2b. Same case as fig. 1 (Mr. T. W.) after delayed second-stage thoracoplasty and lung mobilization. Note final effective collapse and relatively small degree of scoliosis.

as a maximum for any stage. Lateral or oblique roentgenograms are used to supplement the regular P-A exposures of the chest in planning the second-stage operation.

The scapula should be allowed to drop in against the collapsed thoracic cage before the thoracoplasty is considered complete except in the occasional case when the first stage has proved to be sufficient. The patient may complain of considerable discomfort if the inferior angle of the scapula is allowed to override the 6th or 7th unresected rib. Also, if the scapula is held out from the collapsed portion of the thoracic wall

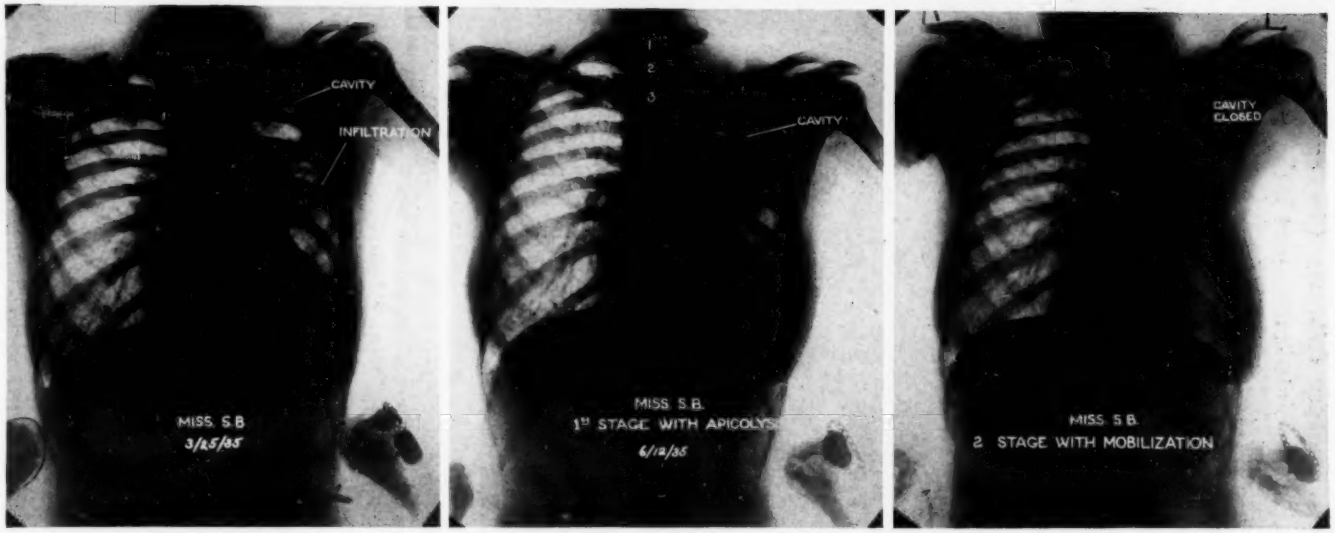

Fig. 3a Fig. 3b Fig. 3c

Fig. 3a. Preoperative roentgenogram in the case of Mrs. S. B. Note very large thick-walled apical cavity which is notably difficult to close by any form of collapse therapy.

Fig. 3b. After first stage. Note that all of the pulmonary tissue has been dropped vertically, now to lie beneath the 4th rib. The patient showed definite improvement after this stage. The second operation was delayed until the maximum in improvement was noted.

Fig. 3c. After second stage with removal of 4th, 5th, 6th and 7th ribs posteriorly and further mobilization. Note the degree of collapse regardless of the delay in stages. The base has been conserved. The cavity was closed without the necessity of an anterolateral or parasternal, or a complete posterior thoracoplasty.

by overriding unresected ribs, the subscapular muscles apparently tend to pull the regenerating ribs back to their former positions, so that the resulting collapse may not close the underlying cavities. Most scapulae will drop in against the collapsed portion of the thoracic wall after a resection of seven ribs. If the resection of a total of five or six ribs is sufficient, the lower tip of the scapula should be resected for a distance of one or two inches, allowing it to fit into the defect of the thoracic cage as after a seven-rib thoracoplasty. Holman (5) has called attention to the value of resection of the scapula in partial thoracoplasty. In cases in which there is a diffuse involvement, moth-eaten cavities or extensive fibrosis below the area of the previous collapse, it may be desirable to provide a more general relaxation of the lung than that given by the complete costatectomy of the upper three ribs and varying posterior lengths of the 4th, 5th, 6th and 7th ribs. In certain of these cases the second and third stages are planned so that shorter posterior segments of more ribs, 8 or 9, are removed. This combines the vertical or apical collapse of the first stage with a paravertebral mid and lower thoracoplasty. The scapula in these cases overrides the lower ribs, thus lessening the deformity and improving the function of the shoulder.

THE TECHNIQUE OF THE SECOND-STAGE THORACOPLASTY

The incision is made in the scar of the first-stage operation, carrying the incision the full length of the scar so that there is an adequate mobilization of the shoulder to expose the brachial plexus and subclavian vessels. The 4th to the 7th ribs are exposed throughout the extent of their posterior two-thirds as well as the area of the previous thoracoplasty. (See figure 4.) It is extremely important to provide adequate exposure of the area previously treated. The attachment of the serratus magnus muscle to the scar in the previously resected area is divided, exposing a shelf of scar-tissue which extends from the 4th rib medially and upward to the brachial plexus. Laterally, the scar is attached to the stump of the 3rd rib, the anterior half of which was not disturbed at the time of the first-stage operation. (See figure 6 in part I.)

The resection of additional ribs is begun with the topmost intact rib and extended down to the 5th, 6th, frequently including the posterior fourth of the 7th rib, and less frequently the 8th rib. The number and length of ribs resected depends entirely on five factors: (1) the extent of the disease in the lung; (2) the degree of pulmonary fibrosis; (3) the present general condition of the patient; (4) the postoperative course

following the first operation; and (5) the course during the second-stage operation. The resection of ribs is carried out from above downward, so that the operation may be concluded at any time without jeopardizing the effectiveness of the collapse.

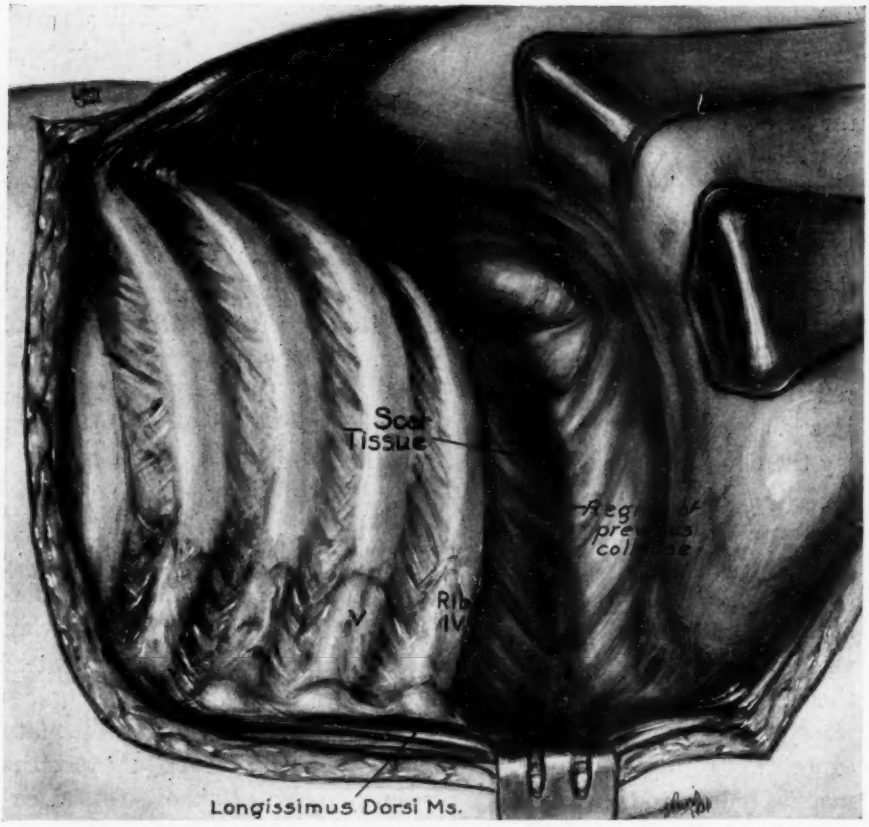

Fig. 4. Exposure necessary for the second-stage thoracoplasty and lung mobilization. The incision is made in the scar of the first-stage operation. The scapula is mobilized, so that adequate exposure of the previous area of collapse is obtained.

The original location of the pulmonary cavities and their size determine largely the length of the ribs to be resected in each individual case. The entire lengths and cartilages of the first three ribs are routinely resected in all cases. The relatively low anterior position of the anterior portion of the ribs makes it unnecessary to resect as great a proportional length of rib from the 4th on down. (See figure 5.)

The third step in the second-stage procedure is the removal of the

anterior half of the 3rd rib. This rib is not completely resected at the first operation, in order to prevent paradoxical movement of the anterior chest-wall after the first-stage operation.

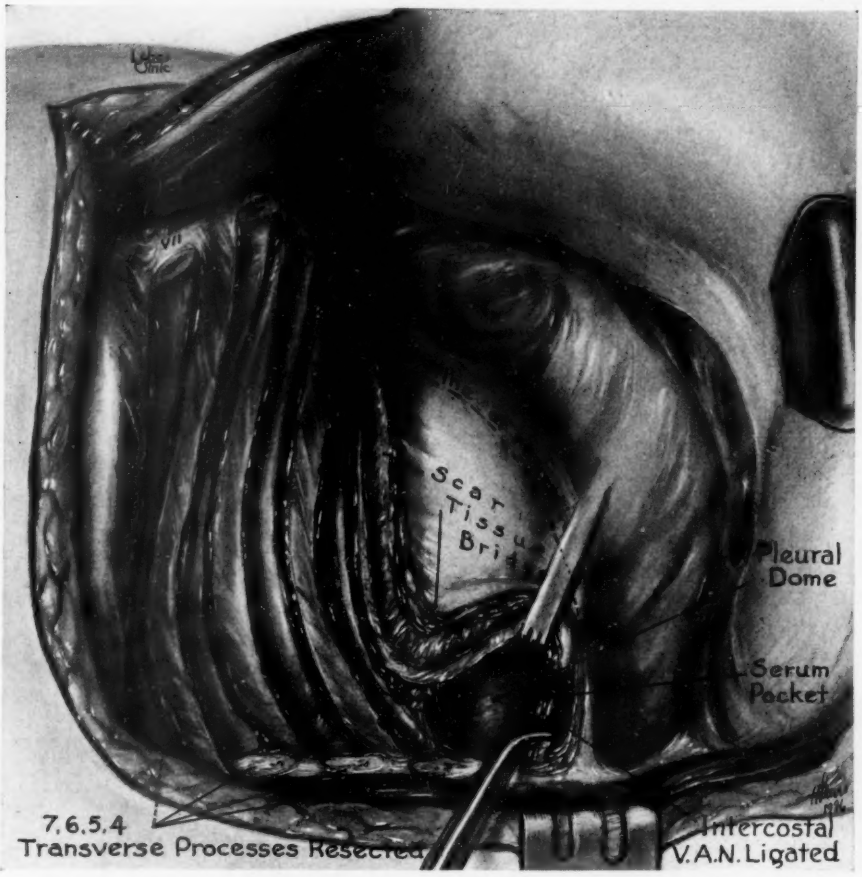

Fig. 5. The resection of the 4th to the 7th ribs has been completed together with the transverse processes. Note the effect of the scar-tissue bridge which prevents satisfactory lateral collapse. The drawing indicates the method of excising this scar and the ligation of the 3rd intercostal vessel and nerve bundle.

The transverse processes of the vertebrae of the resected ribs are next removed. Most apical cavities after apical mobilization come to lie opposite the 4th to 7th vertebrae. For this reason resection of the transverse processes close to the body of the vertebrae is important to aid in obliteration of the vertebral gutter.

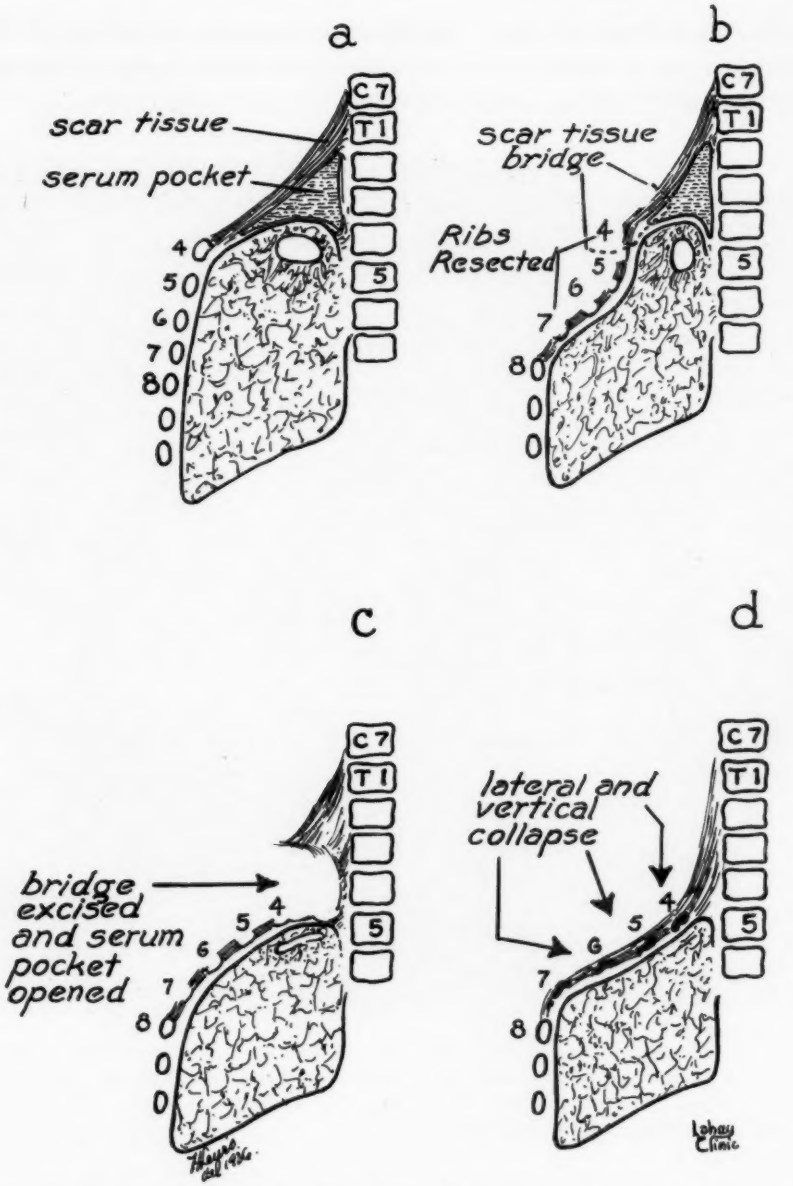

Fig. 6. Diagram illustrating the principles involved in the further mobilization of the lung at the time of the second stage thoracoplasty. a. Relation of new position of apex of the lung to the remaining ribs. The position of a shelf of scar-tissue is shown, beneath which frequently a serum pocket is situated. b. Effect of removal of additional ribs. The scar-tissue acts as a supporting bridge which prevents adequate lateral collapse. c. After completion of lung mobilization, the scar-tissue bridge has been excised. Lateral collapse is now adequate and there is further vertical collapse. d. End-result after second stage, showing new position of chest-wall and regenerated ribs in such a position to prevent vertical re-expansion. Only the periosteum of the first two ribs, part of the 3rd, and occasionally the posterior portion of the 4th is removed.

The next step in the second-stage operation is the completion of the mobilization of the lung which was begun at the time of the first operation. A scar forms in the region of the first-stage thoracoplasty, ex-

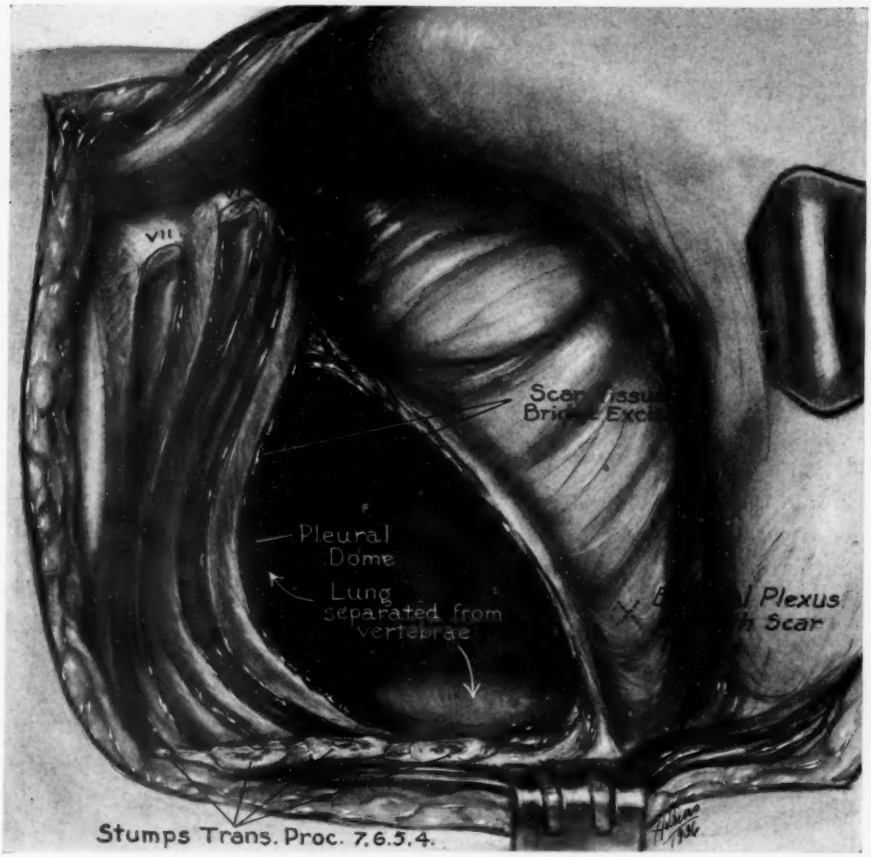

Fig. 7. Completion of the mobilization of the lung at the time of the second-stage thoracoplasty. The anterior stump of the 3rd rib has been removed and the posterior portion of the bridging scar has been excised. This permits the lung to contract further toward the hilum. The vertebral gutter is obliterated. The number of intercostal nerves and vessels divided and the extent of the mobilization of the lung should vary with the size and location of the underlying cavities.

tending from the brachial plexus and bodies of the 1st and 2nd dorsal vertebrae to the periosteum of the 4th rib. (See figure 6.) After the resection of the ribs at the second operation, the chest-wall partially retracts, but is suspended by this scar-tissue and regenerating 3rd rib.

This bridge is divided posteriorly down to the endothoracic fascia, the 4th intercostal vessels being ligated and the nerve divided. A pocket containing serum is usually found beneath the bridge of scar-tissue lying above the apex of the lung and bounded medially by the vertebrae. (See figure 5.) A portion of this bridge of scar-tissue is resected, together with the 4th intercostal muscle bundle, thereby further mobilizing the apex of the lung. (See figure 7.) The 5th intercostal vessels and nerves are divided at times to mobilize the posterior border of the lung down as far as the body of the 5th vertebra. The intercostal muscle bundles of the 5th interspace and below are not removed at this stage.

The first-stage thoracoplasty gives vertical collapse from above downward; the second stage provides mainly lateral collapse of the lung.

Closure of the wound is made as in the first-stage thoracoplasty. Drainage of the wound is never employed. The collections of serum that occasionally occur in the wound are aspirated, the needle being introduced at some distance from the line of incision.

The care given postoperatively is similar to that used after the first stage. Patients are instructed to lie on a folded pillow on their operated side as much as they can with comfort. The importance of this procedure was brought out by Bisgard (6). Shot bags are not applied routinely, but are used if there is paradoxical movement in the anterior chest-wall. Braces or pads applied to the chest have not been used postoperatively. Marked scoliosis has not resulted in these cases. (See figure 12, part I & figure 2, part II.)

THIRD-STAGE THORACOPLASTY

The third-stage thoracoplasty is a separate operation, having definite and distinct indications just as in the first and second operations. There are some patients who will obviously need a resection of more ribs than can be provided safely in two operations. In these cases the operations have been planned so that the degree of collapse resulting from each stage has been about equal. The interval between the second and third stage has usually been about three weeks, provided the condition of the patient is satisfactory. A somewhat shorter interval between the second and third stages than between the first and second stages is desirable in order that the regeneration of the ribs resected at the time of the second-stage thoracoplasty will not interfere with a satisfactory lateral collapse provided by the third-stage operation.

In the majority of cases, a decision cannot be made as to whether

a two-stage thoracoplasty has been adequate for several weeks. In these cases further surgery should be delayed until there is definite proof of persisting open cavities. A resection of one or two ribs, together with a portion of the regenerated ribs of the second-stage thoracoplasty, usually suffices to close the cavity. In a group of 147 patients, treated by thoracoplasty in which mobilization of the upper lobe was not done, a complete thoracoplasty (9 or more ribs) was deemed necessary in 20 instances (14 per cent). In a group of 106 patients treated by the combined thoracoplasty and upper-lobe mobilization, it was necessary to do the complete operation in only 7 patients (6 per cent).

Occasionally, a temporary phrenic-nerve paralysis has been used to close small persisting areas of cavitation. In these cases, however, the cavities were so small that they failed to be demonstrable in the roentgenogram. A positive sputum became negative and the patient avoided a third-stage thoracoplasty.

REOPERATION OF UNSATISFACTORY THORACOPLASTY

Cases of pulmonary tuberculosis that have been subjected to a thoracoplasty and still have an open cavity beneath the area of collapse are seen from time to time. The thoracoplasty failed because that portion of the bony thoracic cage which was removed, however extensive, failed to permit the lung to retract sufficiently to close the cavity. (See figure 11, part I.)

In cases of thoracoplasty failure, the principles of lung mobilization should be employed at the time of revision of the thoracoplasty. Up to the present time, we have found it necessary to carry out a revision in only one case in which lung mobilization had been previously carried out. An incision is made in the scar of the previous posterior upper thoracoplasty and the scapula retracted so that the entire upper third of the reformed thoracic cage is exposed. The brachial plexus and subclavian vessels are dissected out. A portion of the reformed bony thoracic wall is then removed. The resection is usually started at the level of the 4th dorsal vertebra and carried upward to the 1st dorsal vertebra. The intercostal vessels and nerves are ligated close to the vertebral bodies. The apex of the lung is exposed lying in the vertebral gutter with its original attachments intact in the region of the brachial plexus. Sebileau's bands and the posterior vertebral attachments are severed. The lung is then worked down as in the first-stage thoracoplasty. The extent of the procedure carried out in each case depends upon two factors,

namely, on how much mobilization is necessary and upon the manner in which the procedure is tolerated. Two operations may be required. The importance of beginning the revision at the apex and proceeding downward with the mobilization of the lung should be emphasized. This permits a division of the revision into stages if necessary, applying the same principle of collapse as in the original thoracoplasty.

SUMMARY

The principles of the extrafascial mobilization of the lung carried out at the time of thoracoplasty are based upon sound anatomical principles. A resection of overlying ribs alone provides varying degrees of lateral collapse of the underlying lung. A mobilization of the apex of the lung is necessary in order to provide vertical collapse of the lung. The type of collapse obtained by extrafascial mobilization of the lung combined with thoracoplasty simulates that produced by a selective pneumothorax of the upper portion of the lung.

We have employed the operation in 106 cases. Extrafascial mobilization along with thoracoplasty has not increased the incidence or severity of postoperative reactions and the postoperative mortality has not been affected. The percentage of bilateral cases accepted for thoracoplasty has been doubled since the combined operation has been employed. Results have justified the use of the operation as a routine procedure. From our experience to date, lung mobilization with thoracoplasty has provided a more satisfactory collapse of the diseased portion of the lung and there has been a greater conservation of normal lung.

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A REVIEW OF 200 CONSECUTIVE THORACOPLASTIES

R. GLEN URQUHART[1]

Surgical operations in the treatment of tuberculosis endeavor to accomplish only what Nature's efforts have already attempted, and further them by the removal of resisting structures such as bone and cartilage, resulting in immobilization and rest of lung tissue, directly and indirectly altering the lymph and blood circulations, obliterating cavities, and lessening the general intoxication of the body. Clinical observation will disclose that in chronic pulmonary diseases there is the attempt of Nature to diminish the size of the hemithorax by narrowing the intercostal spaces, displacing the mediastinum to the affected side, and elevating the diaphragm. On these facts surgical procedures in the treatment of pulmonary tuberculosis are based.

In uncomplicated cases this is most satisfactorily obtained by the induction of pneumothorax, or by phrenic-nerve operations, resulting in collapse of the lung, elevation of the diaphragm and by thoracoplasty which directly collapses the bony framework of the thorax, resulting in collapse and compression of the lung itself. A distinction should be made here between the term collapse therapy and compression therapy. Collapse therapy is obtained by pneumothorax when negative pressure exists in the pleural cavity and only becomes compression therapy when positive-pressure pneumothorax is used. Thoracoplasty is essentially compression therapy as compared with the collapse therapy of artificial pneumothorax.

As this paper is concerned chiefly with extrapleural thoracoplasty in the treatment of pulmonary tuberculosis and its complications, I will confine the surgical discussion to this procedure.

The first attempt to collapse a tuberculous cavity by the removal of overlying ribs was made by Cerenville in 1885. Numerous other names were connected with this pioneer work at this time. Numerous changes in technique and application have since developed, until to-day the technique most commonly used more nearly approaches that of Brauer, who really popularized this method of treatment.

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It cannot be too often repeated that rest treatment in a sanatorium as well as local rest is just as essential to the patients treated surgically as it is to those who do not come to surgery, particularly when we remember that surgery has only increased our armamentarium for the treatment of pulmonary tuberculosis and has not added anything new to or changed our fundamental ideas as to treatment. It is also borne out by experience that, in many cases of tuberculosis, not only bilateral but unilateral in involvement, by virtue of the distribution, size and consistency of cavities it is physically impossible to collapse the cavities. We have often seen at the autopsy room cavities lying under the sternum or in the posterior gutter which because of their position render them impossible for collapse or obliteration by compression therapy, whichever may be employed. This, we fear, is often a reason why, in spite of what appears to be a satisfactory collapse by X-ray examination, the result is accompanied by the expectoration of positive sputum.

Regarding indications and contraindications of thoracoplasty, we have found that the popular method of numerically tabulating indications and contraindications, except for the teaching of fundamentals to medical students, can no longer be intelligently applied. It has often been emphasized by Archibald (1) and more recently by Lilienthal (2) that standardized methods of therapy cannot be applied to all cases, and operations should be recommended only after a careful study has been made of the individual by both the medical and surgical staffs. I do believe, however, that, whenever there becomes a tendency to disregard certain fundamental principles that have been laid down in the past by those whose experience is greater, unhappy results have become more frequent.

In the selection of cases let us follow the routine course through which a case should go, leading to thoracoplasty. Candidates are usually referred from the medical staff after artificial pneumothorax has been impossible, due either to complete or almost complete obliteration of the pleural space, or when the injected air collapses only the disease-free portion of the lung and has little or no effect upon that portion of the lung which is diseased or in which the cavity is situated. Or again, a large number of patients have had phrenic-nerve surgery (141 in this series), the procedure being either a temporary phrenic operation, which consists of crushing the nerve, or a permanent phrenic operation, which consists of evulsing the nerve. Operations on the phrenic nerve have been performed either after pneumothorax has failed or a combination

of both artificial pneumothorax and phrenic-nerve surgery has failed to bring about the desired result.

Other procedures have also been attempted, such as intrapleural pneumonolysis, extrapleural pneumonolysis or oleothorax, of which there has been only one in this series. This patient died as a result of hiccoughing in seven days. In this particular case, oleothorax had been instituted one year previously at another institution without satisfactory results. Our experience with oleothorax has been extremely limited, as we feel that the indications for this procedure are few. Howlett (3) states that accounts of oleothorax in cases followed over a period of five years are difficult to find in the literature.

Four of the female cases previously had had an intercostal neurectomy as practised by Friederich, Warstat, Bonomo and Alexander. Alexander has studied extensively the results of this operation in the experimental animal as well as in man, and recommends it as a preliminary measure for that group of patients in which the immediate risk of thoracoplasty is too great. Three of these cases later went on to thoracoplasty, one of which died. The other two are apparently arrested, and a fifth case improved so much that thoracoplasty has not been performed and at present the patient is at home much improved. On three cases extrapleural pneumonolysis had been performed, using the bag method (Harvey and Oughterson (4)). Of these three, one is apparently arrested, one much improved and one not improved.

Our cases, after careful consideration at medical conferences, are now studied and discussed at a combined medical and surgical conference. The surgeon's introduction to the case is usually through the medium of the X-ray, which is probably our most important guide to the extent of pulmonary involvement and to a lesser degree to the type of disease. We still feel that the most suitable case for thoracoplasty is that in which the disease is essentially unilateral, or that, if there is disease in the contralateral lung, it must be fibrotic in type and healed or healing. Archibald feels that cases which show a definite tendency to activity, together with a general downward trend of their general condition, are not likely to do well, and should not be considered good risks.

Having accepted a case for thoracoplasty, the patient is then transferred to the surgical ward for observation, which procedure I feel to be of paramount importance, because it is really at this time that the surgical staff can observe the patient and review his complete history, particularly as regards his reaction to previous treatment.

Probably the first consideration should be the general condition of the patient. Contrary to other beliefs, we consider temperature and elevated pulse, both persisting in remaining high, as warning signs to be carefully considered before performing thoracoplasty. They do often indicate activity and should immediately put the surgeon on his guard.

Sauerbruch (5) has pointed out the danger of operating on patients who have evidenced poor resistance and whose general condition does not tend toward chronicity. Certainly, emaciated and cachectic individuals and those with active tuberculosis elsewhere are unsuited to undergo major operations. In this series of cases, the most constant danger signs were dyspnoea and rapid pulse, particularly in patients upon whom

TABLE 1

Sputum and cough

	PREOPERATIVE	POSTOPERATIVE
Sputum:		
Positive	185	22
Negative	15	153
Cough:		
Slight or absent	42	156
Moderate	122	19
Marked	36	0
Expectoration:		
Slight	48	155
Moderate	113	20
Marked	39	0
Haemoptysis	113	8

phrenic-nerve operations had been performed or in individuals whose respiratory functions had been impaired, usually associated with a mild asthmatic condition, silicosis or emphysema. I believe that these signs were present in nearly every case that succumbed, and I feel at this writing that they constitute a real, definite contraindication for thoracoplasty.

Blood, serological and repeated X-ray examinations are necessary, as well as a thorough check-up on all vital organs. This is important, because as expressed by Baer, "Most of our operative methods give rise to fundamental reaction and disturbance of the pathological physiological equilibrium which may be beneficial as far as the diseased lung is concerned, but means ruin to the sum of vital processes which constitute the organism of the patient."

Regarding age, the best results are obtained by thoracoplasty between the ages of 20 and 40. A complete thoracoplasty was performed on a child of 4 for a tuberculous empyema with an underlying lung lesion, and a partial thoracoplasty (Schede) on one other. Both had previously been drained and both are now arrested or cured cases. Thirty-four were operated on between the age of 40 and 50, with 8 deaths. From 50 to 55 there were four cases with one death, and from 55 to 60 there were three cases, aged 57, 58, and 59, respectively, of which all three are apparently arrested. In the older group from 45 up, the apparent age should be the consideration rather than the actual age. If a case over 50 is in good

TABLE 2

Age-group of patients

YEARS	10 AND UNDER	10–20	20–30	30–40	40–50	50–55	55–60
Number of Cases	3	15	84	55	34	4	3
Deaths	0	1	7	8	8	1	0

Duration of disease previous to operation

YEARS	1	2	3	4	5	6	7	8	9	10	12	13	15	16	23	27
Number of cases	12	62	30	30	16	15	12	1	8	7	1	2	1	1	1	1

Elapsed time since operation

YEARS	1	2	3	4	5	6	TOTALS
Cases living	35	53	47	25	9	6	175
Cases operated on	42	61	53	28	10	6	200
Deaths	7	8	6	3	1	0	25

general health with cardiovascular system in good condition and would be considered young for his years, I see no reason why he should not have a thoracoplasty. A categorical fixation of age-limit would have deprived three of our most successful cases of being completely rehabilitated.

In the younger group under 10 or 15, great care should be exercised in the selection of cases, and I believe the operation should be performed only under unusual circumstances. The three children, aged 4, 5 and 16, respectively, are all well, and as yet there is no more tendency toward deformity than in adults. The 4-year-old child was markedly deformed from her long-standing empyema, and is now much straighter, and growth progresses much more satisfactorily than before operation.

What the result will be in 20 years I do not know, but I feel certain that, had these children not been treated surgically, in at least the two with empyema, changes which are associated with long-continued suppurative processes would have claimed their lives in the near future.

Regarding sex, statistics show that approximately the same number of women as men have been subjects of thoracoplasty and the results are approximately the same in both. In this series there were 30 more women than men,—115 females with 13 dead and 85 males with 12 dead. There were 3 Negroes and 197 whites. All 3 Negroes have done well, two being discharged apparently arrested and one still in the institution showing improvement.

It is surprising to me that results of operations on the left side are very much more satisfactory than those upon the right side. Peter Bull, of Oslo, states that the immediate risk of operation is considerably greater for men than for women and that the operation is three times more dangerous for right-sided than left-sided cases. In this series, there were 90 right and 109 left, with one bilateral thoracoplasty. Fifteen of the rights are dead, and 10 of the left. We do feel that the right-sided cases tend to have a stormier time postoperatively than the left-sided.

Probably the most important preoperative requisite is a fixed mediastinum, which actually means a stiffening of the mediastinal pleura. The most constant indication of a fixed mediastinum is the displacement of the trachea toward the affected side as seen by X-ray. Removal of the ribs in the absence of a fixed mediastinum is frequently attended by paradoxical movement of the underlying lung, which interferes with the heart action resulting in mediastinal flutter. Methods of artificially fixing the mediastinum by means of injections of acacia and paraffin oil, etc., are still in the experimental stage, and as yet have not been used to any very great extent in man.

The vast majority of our patients in this series have had symptoms of pulmonary tuberculosis for from two to nine years, and in some instances as many as thirteen and sixteen years. No doubt the presence of disease for this length of time would automatically place them in Archibald's "Good Chronic Group," but I fear that many of these patients are the remains of a very much larger group, which has passed on because an opportunity for receiving surgical treatment was available to only a very few patients up until eight or ten years ago. Patients who have had their disease under one year should be very carefully selected, because we do know that chronicity is a very necessary entity for the patient

to possess. However, I believe that chronicity should be determined more by the appearance of fibrosis rather than actual months or years. Artificial pneumothorax has been attempted in practically all cases before surgical intervention.

I would rather, because of its importance, consider the better lung first. Collapse and compression therapy were originally based upon the assumption that the contralateral lung be free from active progressive disease. This assumption has been subject to considerable change recently, with the advent of bilateral artificial pneumothorax, phrenic operations, and a combination of both. Frequently, bilateral cases eventually become

TABLE 3

Deaths

TIME	DEATHS		CAUSES	CASES
		per cent		
48 hours	4	2	Respiratory failure	2
			Cardiac failure	2
10 days	7	3½	Cardiac	5
			Kidney	1
			Hiccough	1
1 month	7	3½	Acute spread	2
			Pneumonia	5
2½ months	1	½	Tuberculous pneumonia	1
4 months	2	1	Spread of disease	2
15 months	1	½	Empyema	1
20 months	1	½	Contralateral spread	1
2 years	1	½	Automobile accident	1
3 years	1	½	Pulmonary embolism	1
Total deaths.....	25	12½		

suitable candidates for thoracoplasty, following the clearing up of the disease on one side or when the disease is confined to the apices of both lungs. A series of cases has been treated by bilateral thoracoplasty by Allen (6) with satisfactory results. In our series one case has been thus treated with satisfactory results.

It has frequently been observed that lesions in the better lung often heal following collapse of the more diseased lung. This result also frequently occurs in thoracoplasty. While I do not believe that pulmonary tuberculosis is ever completely unilateral, active progressive lesions in the good lung should be considered unfavorable for operation because we are unable to foretell accurately whether or not the disease in the better

lung will progress after operation. In this series there are 113 cases with evidence of healed disease in the good side and 11 with disease in more than one lobe, while death was caused in only 11 cases by either tuberculous pneumonia or spread of involvement in the same side or to the opposite side.

In considering the worse lung, extensive disease of all lobes is not considered to be a contraindication to operation, keeping in mind of course the patient's general condition. Cavity was present in 174 of the 200 cases, and in those living 20 are still open. I believe we all feel that the type of lesion, as to whether it be chronic, fibrous and productive, or

TABLE 4

Results

	TOTAL	DEAD		
Males	85	12		
Females	115	13		
Whites	197	25		
Negroes	3	0		
			STILL OPEN	CLOSED
Cavities	174	19	20	135
Phrenic	141	0		
			STILL OPEN	APPARENTLY ARRESTED
Empyema	19	1	5	13
			ABSORBED	NOT ABSORBED
Fluid	14	0	13	1

whether it be exudative and progressive in type, is of great prognostic value. For this reason a persistently elevated temperature is usually the sign of an exudative type of lesion and the patient should not be subjected to surgery while he is febrile.

Alexander (7) does not believe that the amount of sputum has much effect upon the indications or contraindications for operation. Nor does haemoptysis contraindicate operation. However, in this latter condition it is advisable to use a local anaesthetic in these cases, as is our practice here. If there is a cavity in the base, we elect to operate from below up, and *vice versa* when the cavity is in the upper hemithorax. In 113 cases there was a history of blood-spitting before operation and 8 have raised

blood since operation. One case had a severe haemoptysis while on the table from a basal cavity. Extraction of blood-clot and artificial respiration had to be employed because of asphyxiation. The remaining stages were performed under local anaesthesia, during which no haemorrhage was encountered. At present the patient is at home and working. Large severe tuberculous empyemata that persist in spite of conservative treatment should be operated upon by thoracoplasty as early as possible. Long-continued irrigation is usually followed by sinuses and tuberculous infections of the pleura and soft tissues through which the aspirating needle passes. In uncomplicated tuberculous empyema with an underlying lung lesion, thoracoplasty should be performed accompanied by aspiration. When the infection is mixed, it is often advisable to drain before a thoracoplasty which may or may not be associated with a Schede type of operation. In this series there were 19 empyemata, 13 of which have been cured, 5 are still open, all requiring further surgery, and one is dead.

Fluid, on the other hand, requires no treatment other than aspiration previous to operation. However, aspiration of fluid should continue between stages, and after the operation is complete and as long as there is any tendency for the fluid to reform. In 14 cases of fluid, absorption occurred in all but one.

After all the above facts are taken into consideration, the patient now goes under a period of observation in the surgical ward, during which time a careful and thorough examination of the cardiovascular system is necessary, as this system is next in importance to the actual condition of the lungs. Any evidence of inefficiency should be carefully considered along with the other systems.

There was no evidence of bone or joint disease in any of this series, but tuberculous laryngitis was present in 7 cases, four of which were quite severe. The larynx was treated by means of cauterization in 6 cases either before or during operations. Apart from a very acute fulminating laryngitis, there seems to be a tendency, as is found in pneumothorax therapy, toward healing, as we have frequently seen a large number of cases clear up after the diseased area has been controlled and cavities closed. Tuberculosis of the intestines and renal tuberculosis are considered, for the most part, as contraindications for thoracoplasty.

As stated before, dyspnoea which is accompanied by a low vital capacity is a contraindication to thoracoplasty. However, our present methods of determining vital capacity with instruments requiring forced

inspiration and forced expiration are unsatisfactory in dealing with tuberculous patients. In the first place, intelligent patients are loath to coöperate in this test because of fear of injury, which attitude I am entirely in sympathy with. In the second place, tests carried out by Campbell (8) demonstrated that, with the exception of one patient in his series of bilateral pneumothorax cases, the vital capacity was less than 50 per cent of normal; yet none of the patients complained of dyspnoea. It is our opinion, therefore, that at present our best indication of this condition is shortness of breath on slight exertion, after coughing, or following other collapse-therapy procedures.

Our ideas regarding pregnancy associated with the surgical treatment of tuberculosis are definitely changing, and I do not believe that we can consider it a serious complication as far as the mother is concerned. Our experience, however, is limited to two cases. In one case, in which the patient was three months pregnant when thoracoplasty was commenced, delivery and child were normal, and the mother is definitely improved. The second case was operated on six weeks after delivery, and is at present an apparently arrested case, at home, and doing her own housework. Pregnancy, when it is present in a patient fortunate enough to be in a sanatorium, responds unusually well under rest, pneumothorax and the more minor surgical procedures. Immediately following delivery is the time when expert handling of the patient is most important, and for this reason I believe that the patient should be delivered in a sanatorium, particularly when the institution is as well equipped as those in Connecticut are.

I feel that the most satisfactory way to present our cases is by dividing them into three groups according to their operative risk. Archibald (9) has done this in his series, thus prompting our adoption of this method. In group 1 are the favorable cases, uncomplicated cases and good chronics; in group 2, the doubtful or conditionally favorable cases; and in group 3, the definitely unfavorable cases.

Unquestionably, if only group-1 cases had been considered for thoracoplasty to the exclusion of group 2, a large number of patients would have been deprived of a reasonable opportunity for recovery. In this series, there were 54 such cases with 24 apparently arrested, 20 improved, 4 unimproved, and 6 dead. We know that, if the patients in group 2 had not been operated upon, it is doubtful if any would now be arrested cases. The 20 improved, I feel sure, will for the greater part be regarded in the near future as arrested, and I doubt if any of us could deny that at

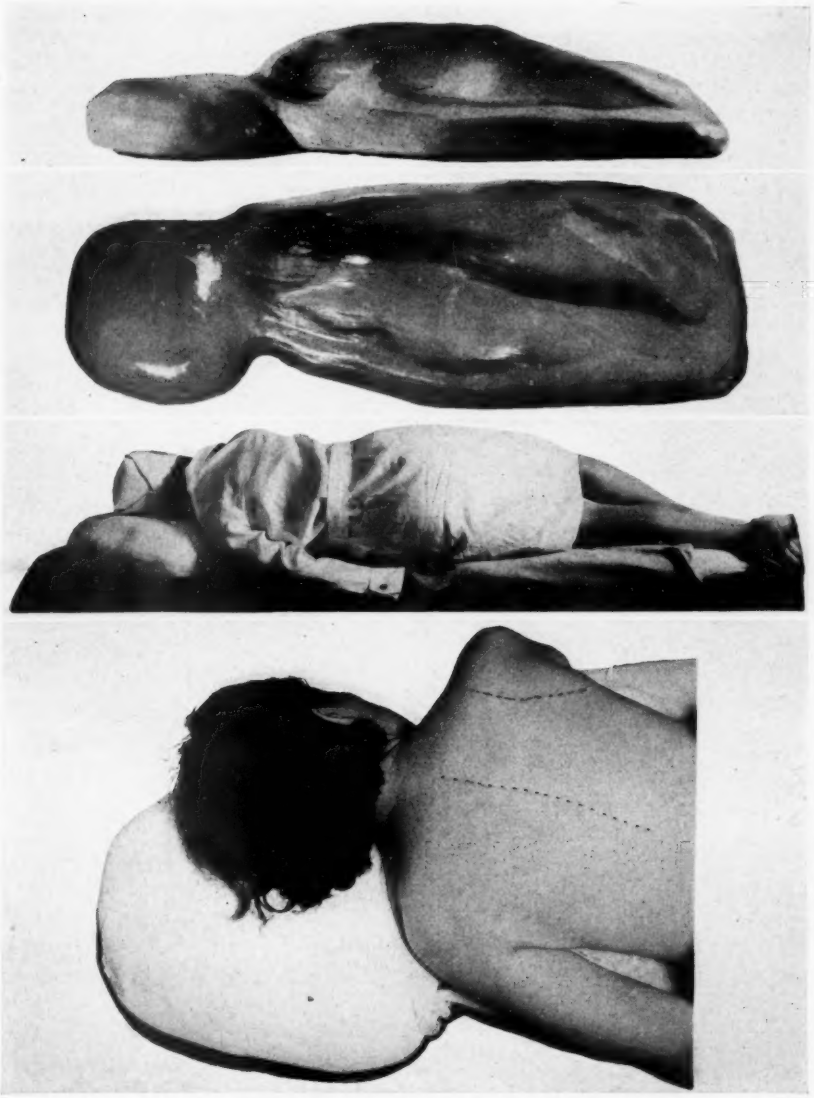

FIG. A

FIG. B

FIG. C

FIG. D

FIG. A. Cast of cork mold for adjusting position of patient—horizontal view
FIG. B. Cast of cork mold for adjusting position of patient—vertical view
FIG. C. Cast of cork mold for adjusting position of patient; nurse posing for leg position
FIG. D. Cast of cork mold for adjusting position of patient; close-up of head position
For description of mold see text

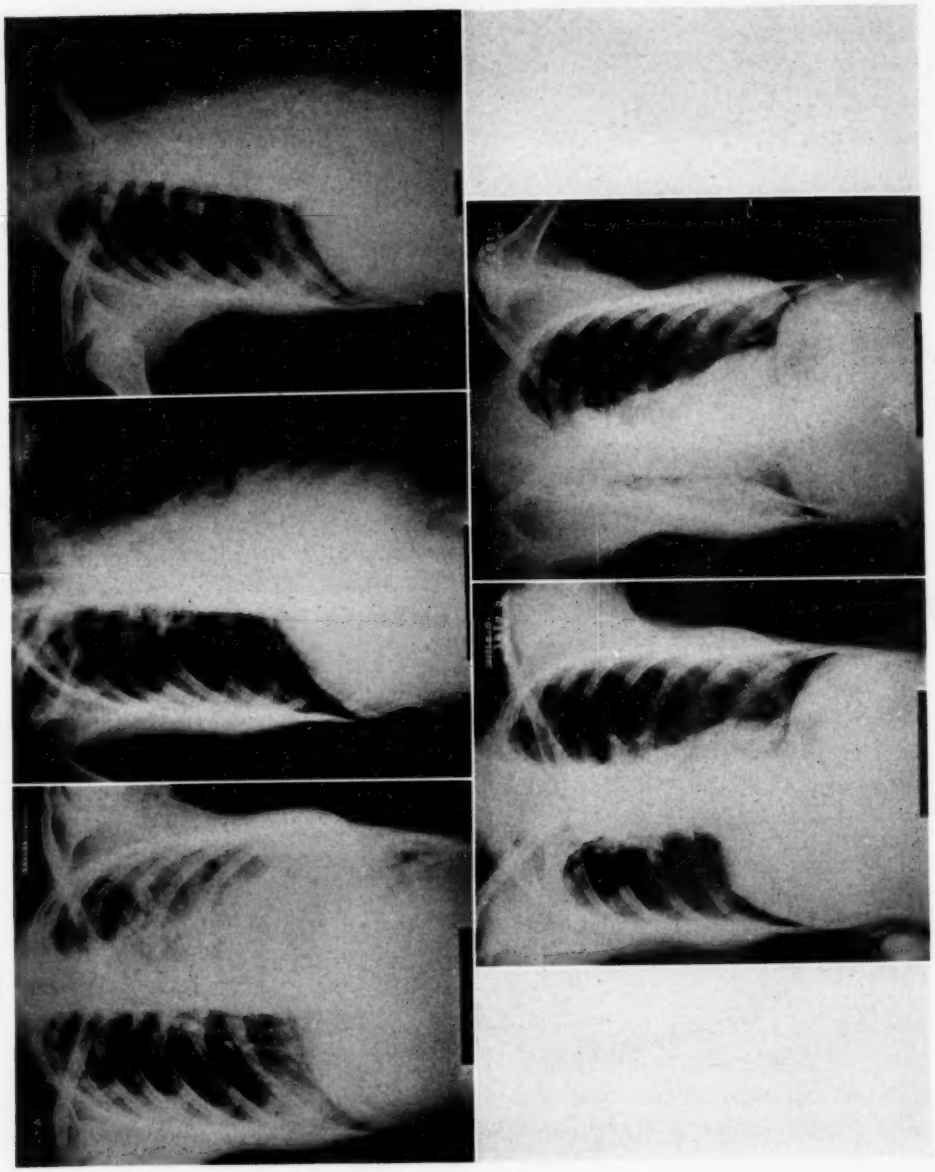

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

least some of the 6 deaths would have occurred without surgery. It is reasonable to assume that the "not-improved group" would also be unimproved. Regarding group 3, I also feel that the results in this group are encouraging with 8 out of 31 "apparently arrested," 9 improved and 14 dead. I am certain that, had these 31 patients not been operated upon, there would be many more than 13 deaths. While this operation should not be resorted to in the face of certain failure, a reasonable chance for recovery with the patient's full understanding of the situation makes the operation justifiable in certain selected cases.

Preparation of the patient for operation is divided into, first, the general preparation, which consists of becoming acquainted with the patient and gaining his confidence, not only in the surgeon but in the procedure itself; and, second, the preoperative routine. It has been a rule in this department that patients are never operated upon until they themselves really want the operation done, and to hold off any cases until he or she is

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FIG. 1. Case 1. Preoperative plate showing extensive involvement of left lung with large cavity in left upper lobe. Also healed disease in right upper lobe.

FIG. 2. Case 1. Following complete thoracoplasty in seven stages. Collapse not satisfactory.

FIG. 3. Case 1. Reoperation of eight upper ribs in two stages. Satisfactory collapse.

FIG. 4. Case 2. Before thoracoplasty.

FIG. 5. Case 2. After thoracoplasty. Three stages.

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absolutely "sold" on it. I think we all have come to realize more and more the necessity of a hopeful and restful attitude on the part of the patient previous to operation. The patient should be visisted in an informal manner by the surgeon the evening before, to reassure and encourage the individual.

The immediate preparation of the patient consists of a cathartic two nights previous to operation. On the day before, the patient is put on a liquid diet and encouraged to force fluids, which have been sweetened as much as is compatible with proper digestion. A sedative is administered the night before operation to ensure a good night's rest (veronal, amytal, etc.), and all fluids are stopped six hours before operation. About two hours before operation, a combined dose of morphine, gr. $\frac{1}{4}$, and atropine, gr. $\frac{1}{150}$, is administered, and the patient is encouraged to completely drain his lung by postural drainage, thereby guarding against aspiration of infected secretions.

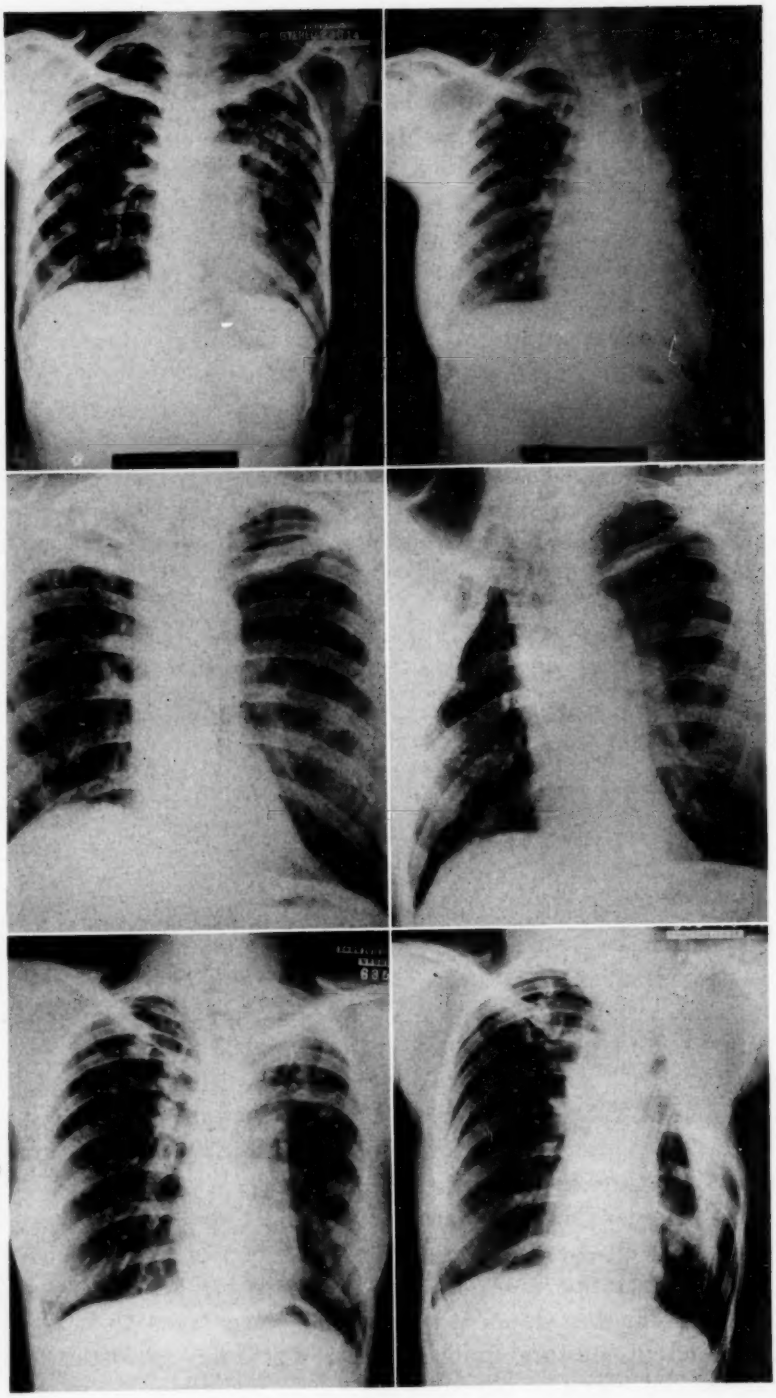

FIG. 6

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 11

It has been our custom to use, as a basic anaesthetic, avertin in doses never exceeding 80 mgm. per kilogram of weight. This is supplemented on the table with 0.5 per cent novocaine, and, if necessary, a small amount of nitrous oxide. We have used avertin for over eight years as a basic anaesthetic with complete satisfaction. When we first started to use this anaesthetic, we were warned by Harvey (10) against giving higher than an 80 mgm. dose, because of the fact that this dose occasionally resulted in surgical anaesthesia. We feel that avertin is a great boon to tuberculous patients, because they go quietly to sleep in their own room, often not awakening for several hours after returning to their room. Another advantage of this anaesthetic is that a very much smaller amount of a supplementary anaesthetic is required. An intratracheal tube has been used in the majority of our cases in the past two years. It may be easily inserted with the addition of a small amount of nitrous oxide and oxygen.

FIG. 6. Case 3. Before thoracoplasty.
FIG. 7. Case 3. After three-stage thoracoplasty.
FIG. 8. Case 4. Before thoracoplasty. Lesion limited to the upper lobe.
FIG. 9. Case 4. After two-stage partial thoracoplasty. Five ribs.
FIG. 10. Case 5. Before thoracoplasty. Showing lesion limited to left upper lobe.
FIG. 11. Case 5. Following partial thoracoplasty in two stages. Seven ribs removed.

Obtaining a satisfactory position of the patient on the table has been simplified by the use of a specially constructed mold of mine which is demonstrated (figures A to D). The mold is made of cork covered with canvas. Comfortably strapped to this mold, the patient's scapula is quite naturally thrown far outward, and its position alone prevents any change in posture of the arm in question.

The preparation of the skin is important, because wound infection is a grave complication which sometimes follows operation. The whole back should be prepared carefully by removing all hair and scrubbing with ether and alcohol. A final coat of some antiseptic may be used.

As previously stated, the operation is usually commenced at the top because the disease is most frequently located in the upper part of the chest. Three ribs are resected at the first stage, which is through a paravertebral incision, swinging well laterally below the scapula. This wound is reopened for the second stage ten to fourteen days later if the patient's condition is satisfactory, and the next 4 ribs removed. The lower 4 ribs are removed through a second incision ten to fourteen days

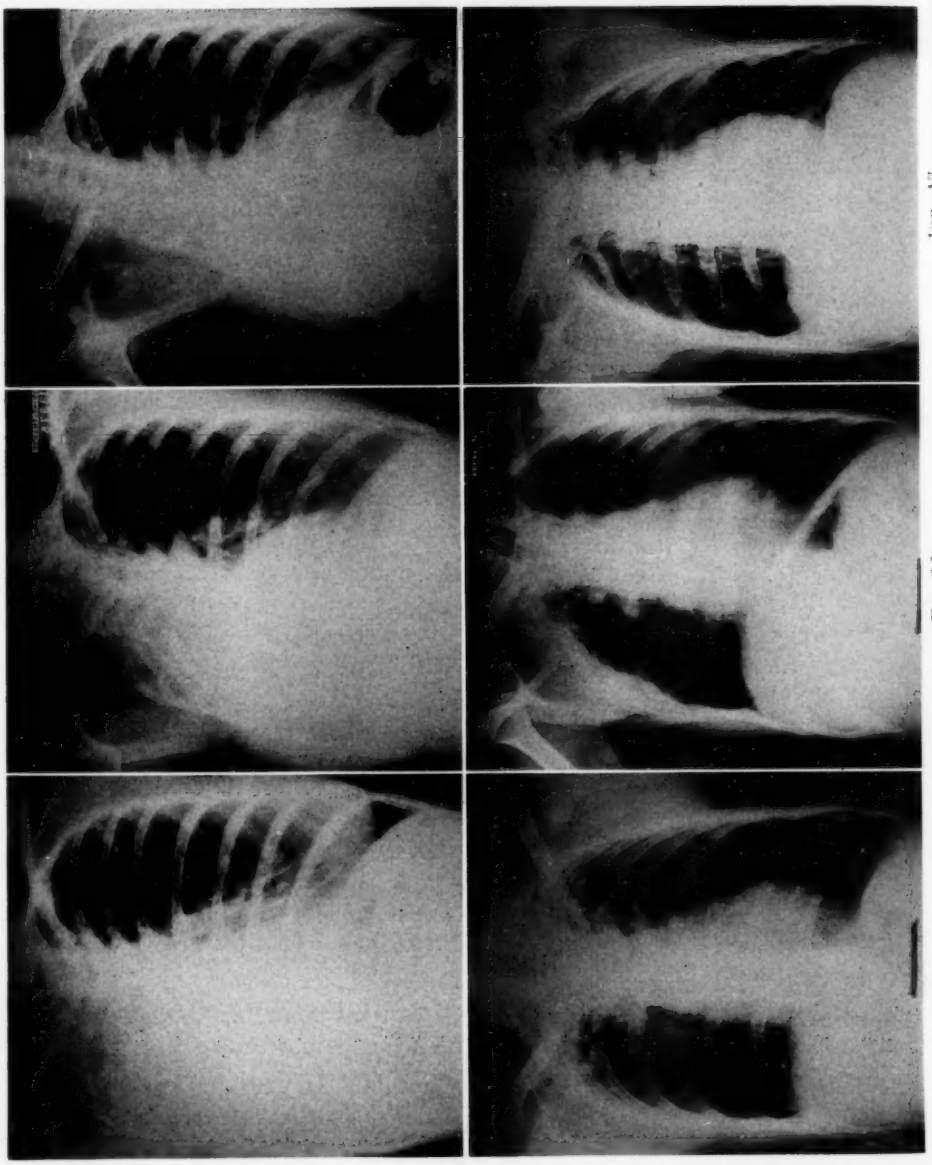

FIG. 12

FIG. 13

FIG. 14

FIG. 15

FIG. 16

FIG. 17

later. We feel very keenly that this operation should never be performed in less than three stages, and as many more as the patient's condition or reaction to the operation warrants. All of the 1st and 2nd ribs are removed and practically all of the 3rd rib, posteriorly to and including a part of the transverse processes. About three-quarters of the 4th and 5th ribs are removed, and then tapered down to the 11th, of which only 3 to 4 inches are necessary to resect.

Great care should be given to haemostasis, while the large muscles of the back are being divided, as we feel that the prevention of blood-loss during operation prevents postoperative shock and the necessity for transfusions. Only two such procedures were necessary in this series of cases. Intravenous injections of glucose and saline solution are frequently given. As soon as the patient is returned to the room, a rectal drip, consisting of tap-water with one dram of soda bicarbonate to the quart, is given at the rate of about 20 drops per minute. The patient

FIG. 12. Case 6. Before thoracoplasty.
FIG. 13. Case 6. Following complete thoracoplasty. Result unsatisfactory.
FIG. 14. Case 6. Following reoperation, four years later, in two stages. Upper nine ribs removed.
FIG. 15. Case 7. Showing bilateral upper-lobe involvement.
FIG. 16. Case 7. Right upper five ribs removed in two stages.
FIG. 17. Case 7. Bilateral thoracoplasty. Right upper five and left upper four ribs removed.

frequently absorbs from one to three litres in 24 hours by this method. The patient is turned toward the operated side, and sufficient morphine administered to keep him comfortable. The wound is never drained, as we feel that this procedure invites infection. If the ooze is sufficient to embarrass respiration, this is released from the wound by the careful insertion of a haemostat into the wound. The Murphy drip is continued until fluids are safely taken by mouth usually within 12 to 24 hours.

Regarding operative complications, we have been extremely fortunate in never encountering any severe bleeding, and on only four occasions was the pleural cavity opened, but without any bad results. Before closing, however, the wound, particularly the lung surface of it, should be absolutely dry. The muscles are closed in layers with fairly closely spaced interrupted catgut sutures. To prevent haemorrhage, we prefer using a subcutaneous continuous suture to stay sutures. The wound is covered with silver foil, which ensures a dry dressing.

As previously stated, the amount of collapse does not always depend upon the amount of rib removed, but to a greater extent upon the condition of the underlying cavity walls and lung parenchyma itself. This often prevents a satisfactory collapse; and, while improvement takes place, secondary operations are necessary to obtain a satisfactory collapse. Ten of our cases required reoperation, in which all of the vertebral portion of the rib, together with the transverse processes and regenerated ribs, were removed. Eight of these cases now have a negative sputum. It has also been necessary to perform 21 anterolateral operations, and in one case the removal of the medial half of the sternum. Since we have

TABLE 5

Partial thoracoplasties

	NUMBER OF RIBS REMOVED				
	4	5	6	7	8
Number of patients	4	3	12	21	1

	BEFORE OPERATION	AFTER
Sputum:		
Positive	39	2
Negative	2	39

	APPARENTLY ARRESTED	IMPROVED	NOT IMPROVED
Result	33	6	2

	GOOD	FAIR	POOR
Rehabilitation	28	7	6

been dividing the serratus anterior muscle according to Alexander's (11) method, anterolateral operations have been required very much less frequently.

Regarding partial thoracoplasty, from our results I feel that this operation is the most satisfactory method that we have for treating apical disease and apical cavities. While partial thoracoplasty may be decided upon before operation, the number of ribs to be removed or the operation itself may have to be abandoned, because of the tendency at times for the apex of the lung, together with its contained cavity, to be displaced downward to such an extent that a complete thoracoplasty may

have to be performed in order to obtain a satisfactory collapse. There were 41 partial thoracoplasties in this series, with the removal of from 4 to 8 ribs. Cavities and positive sputum were present in 29 cases, and two had negative sputum. At the present time cavities are closed, and the sputum is negative in 39, while 2 still remain positive.

TABLE 6

Rehabilitation

Rehabilitation good	87
Rehabilitation fair	18
Rehabilitation uncertain	14
Total patients discharged apparently arrested	119
Ready for discharge	20
In sanatorium improved	27
Too early to decide	5
Worse	4
Dead	25
Total	200

TABLE 7

Summary: 200 cases: 542 operations

GROUP	CASES	APPARENTLY ARRESTED	IMPROVED	NOT IMPROVED	DEAD	TOTAL
A	115	87 (75.6%)	19 (16.5%)	4 (3.5%)	5 (4.4%)	100%
B	54	24 (44.4%)	20 (37.2%)	4 (7.4%)	6 (11.0%)	100%
C	31	8 (25.9%)	9 (29.0%)	0	14 (45.1%)	100%
Total	200	119	48	8	25	200
Percentage		59.5%	24.0%	4.0%	12.5%	100%

For the past four years it has been our practice to fit the patient with a two-inch-thick sponge-rubber jacket, as suggested by Dayton (12), which is held in place by a snug-fitting binder with shoulder-straps. In addition, sandbags up to 15 pounds, are used for the first three months, after which the patient is allowed up, but continues to wear the sponge-

rubber jacket for an additional three months. We feel that the regenerated bone which has reformed is by this time solid enough to prevent reëxpansion of the lung, and also that a very much better collapse is secured by the use of this jacket, because of the constant pressure it exerts for 24 hours a day on the chest-wall. This jacket is applied after the wound has healed.

By rehabilitation, I mean to classify patients who are able to do ordinary work as *good*, only light work as *fair*, and little or no work as *poor*. Likewise, I do not like the term "cure" used in reporting results of surgery in tuberculosis. In general surgery, such as operations for acute appendicitis, or gall-bladder disease, etc., the term "cure" may be suitably applied; but, in my experience with not only the surgical but the general clinical treatment of tuberculosis, I believe the term "apparently arrested" is much more appropriate, and would tend to be less confusing to those whose work is confined to the clinical or medical treatment of tuberculosis. When we say a disease is "cured" we mean that there is no possibility of the return of the symptoms or of the disease itself; but those of us who have had long experience in the treatment of this disease know that there is a very great tendency toward reactivation and recurrence of symptoms if a patient is subjected to an improper environment or other unsatisfactory conditions. An analysis of the 25 deaths occurring in this series brings out the importance of the proper selection of cases, and demonstrates often the inability with the present means and methods at our disposal to accurately forecast the reaction of all of our patients to thoracoplasty.

While the late results of many of these cases will no doubt change as time goes on, and while some of our good results at the present time may be reversed later on, I have tried to give you an unbiased picture of this group of 200 cases as it appears at the present time, and it is my earnest belief that most of the cases that are not now in the "apparently arrested group" will, as time goes on, take their places among the "apparently arrested."

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COMPLICATIONS OF SUCCESSFUL THORACOPLASTIES[1]

ARTHUR H. AUFSES

During the past decade there has been a tremendous increase in the number of patients with pulmonary tuberculosis who have been treated by rib-resection with an arrest of their disease process. Present day statistics show that from 40 to 60 per cent of thoracoplasties are successful in permanently arresting the course of pulmonary tuberculosis. A case to be considered as clinically cured must have no demonstrable cavity and a negative sputum. A better knowledge of the pathological lesion which lends itself to cure by surgical methods, together with the use of special types of thoracoplastic operations, has steadily added to the number who have been rehabilitated and returned to a normal livelihood.

Thoracoplasty, as performed at present, entails very extensive rib-resections as compared with the former Sauerbruch paravertebral operation. Such wide decostalization causes a marked change in the form, position and physiology of the intrathoracic organs, as well as structural deformities in the thoracic cage itself. Some of these changes may not make themselves manifest until long after the patient has lost contact with the surgeon. The phthisiologist and family physician should have a knowledge of the complications which may occur and which may be a source of great discomfort to the patient.

SCOLIOSIS

Diseases of the intrathoracic organs or of the thoracic cage quite commonly cause curvature of the vertebral column. Marked fibrosis, occurring in the lung, as is found in chronic pulmonary tuberculosis, is usually accompanied by changes in position of the intrathoracic organs as well as by deformities of the thoracic cage. A chronic fibrotic pulmonary lesion will gradually tend to narrow its half of the chest, and will produce a contracture of the ribs with narrowing of the intercostal spaces, and later will draw the mediastinum, heart and trachea to the affected side. The mediastinum is in close proximity to the vertebral

[1] From the Surgical Division, Montefiore Hospital, Dr. A. A. Berg, Chief of Division, and the Tuberculosis Division, Montefiore Hospital, Dr. Harry Wessler, Chief of Division.

column and in many cases is fixed to the vertebrae by fibrotic connective tissue. Any force acting upon the mediastinum is transmitted to the vertebral column, causing a lateral scoliosis with its convexity to the affected side.

Vertebral curvatures are more liable to occur in youth when the spine is still in its formative period. Similarly, the severe postoperative deformities are found in patients under eighteen.

In view of the fact that thoracoplasty is usually performed for predominantly fibrotic pulmonary tuberculosis, one would expect a good percentage of "thoracoplasty cases" to have a scoliosis before operation. Bisgard (1), in 101 cases upon whom extrapleural thoracoplasty was performed, found 53 had straight spines before operation and 48 had curvatures.

Rib removal, by interfering with the normal balance of opposing bony and muscular forces, causes a scoliosis with the convexity toward the operated side. The nearer the resection to the spine, the greater the deformity will be. In thoracoplasty, the posterior ends of from five to ten ribs, usually with parts or all of the transverse processes, are removed. Furthermore, the *erector spini* group of muscles may be injured or paralyzed due to injury to the nerves supplying them. Kinsella (2) and and Semb (3) believe that paralysis of these muscles is an important factor in the development of scoliosis. Arnd (4) produced scoliosis in animals by unilateral removal of this group.

That thoracoplasty does have a definite effect upon the spinal column has been shown by Bisgard (1). In a group of 131 cases, extrapleural thoracoplasty was performed in 101 and some type of Schede operation in 30. Fifty-one of these cases had straight vertebral columns before operation. These were invariably scoliotic after operation with the convexity toward the operated side. In 21, in which there was a scoliosis with convexity toward the affected side before operation, there was a definite exaggeration of the deformity postoperatively. In 51 with anteoperative convexity to the unaffected side, 12 were partially or completely corrected by operation and 39 were overcorrected with resulting opposite scoliosis. Of 101 thoracoplasties, only two had straight spines postoperatively.

If scoliosis does develop, it frequently manifests itself within a few weeks after rib-resection, and it is during this period that active treatment is indicated. Once there is new bone-formation from the periosteum and rib-ends, we have a stabilizing factor which tends to minimize

any further deformity. Exercises instituted soon after operation, aided by braces, are means of preventing lateral curvatures. Bisgard uses postural wedge compression by having the patient lie on the affected side immediately after operation, with a pillow rolled beneath his thorax opposite the point at which the apex of the deformity might be expected.

Where a Schede operation is performed with removal of parietal pleura, periosteum and intercostal tissues, the stabilizing effect of newly regenerated bone is lost. Fortunately, it is more common to find "pleural scoliosis" with the convexity to the unaffected side in those cases which will require a Schede procedure. It is this type of scoliosis which tends to be corrected by a wide rib-resection and, therefore, many of these cases will eventually have a fairly straight spinal column.

In the performance of thoracoplasty, the clavicles are permitted to remain intact and thereby preserve the shoulder girdle. In patients over eighteen years, the great majority of vertebral curvatures resulting from rib-resection are of moderate degree. When clothed, it is difficult to perceive that they have undergone extensive decostalization. Except for those few patients in whom the development of a very marked scoliosis will have a bad effect upon the heart or mediastinal organs, the average case will not suffer any great physical injury. A resulting scoliosis is not too great a price to pay for the arrest of pulmonary tuberculosis.

FIXATION OF THE SCAPULA

The completion of a Sauerbruch paravertebral thoracoplasty has rarely had any effect upon the mobility of the shoulder. Since partial upper thoracoplasties with wide subscapular rib-resections have become a popular method of treatment, it is more common to find some impairment of scapular function. If a wound infection of the subscapular area occurs, the scapula may become fixed to the intercostal tissues by the scar-tissue that ensues. Furthermore, when only 5 or 6 upper ribs are removed, the angle of the scapula may become fixed under the next intact rib. This fixation of the scapula may cause some impairment of shoulder function and may require removal of one or two more ribs in order to restore mobility of the scapula. Numerous surgeons advocate removal of the inferior border of the scapula during an upper thoracoplasty in order to prevent the occurrence of this complication.

The medial border of the scapula has also been found to give pain, due to rubbing against the transverse processes and vertebral bodies after

FIG. 1

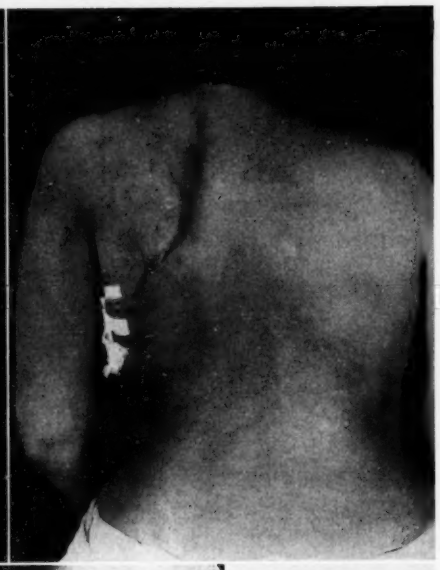

FIG. 2

FIG. 3

FIG. 1. D. H., no. 26,419: Marked scoliosis in girl of 29, following complete thoracoplasty with successful arrest of tuberculosis.

FIG. 2. E. K., no. 21,439: Partial thoracoplasty complicated by wound infection, with fixation of the scapula in elevated position.

FIG. 3. A. K., no. 26,627: Bronchiectasis of lower lobe in patient with single large apical cavity.

wide rib-resection. Resection of the medial half of the bone has relieved the symptoms. (Steinke (5).)

CARDIAC HYPERTROPHY

Sauerbruch states that enlargement of the right side of the heart occurs during all forms of collapse therapy. The occurrence of hypertrophy and dilatation of the right heart has been known to be due to pulmonary fibrosis and obliteration of the pleural space. (Moschowitz (6).) That they can occur as a result of the fibrosis developing during the course of pulmonary tuberculosis has been well established clinically. Following thoracoplasty, we may have as much as 50 per cent of the pulmonary tissue reduced to a hard, fibrotic mass. This offers a considerable resistance to the passage of blood through the pulmonary circulation. In the presence of such pathological involvement, some degree of right-sided cardiac hypertrophy must be an inevitable sequel. That this train of events does not more often progress to dilatation and eventual cardiac failure is probably due to the fact that, after a successful thoracoplasty, the pulmonary lesion fibroses until it is arrested. With the cessation of the active disease process, no further fibrotic changes will appear in other areas. The moderate cardiac hypertrophy which develops is sufficient to overcome this resistance in the pulmonary circulation and an equilibrium is reached, which may continue for many years.

BRONCHIECTASIS

It is only since the advent of lipiodol bronchography that the frequent occurrence of bronchiectasis in pulmonary tuberculosis has become evident. As this diagnostic procedure is becoming a popular method, one finds that bronchiectasis not only occurs after thoracoplasty but is also present in many unoperated cases of chronic pulmonary tuberculosis.

Brauer (7) has never observed a single case of dilatation of the bronchi resulting from long-continued pneumothorax therapy. Without the use of bronchoscopy and lipiodol, a bronchiectasis might very well remain undiagnosed. Figure 3 shows a widespread bronchiectasis in the lower lobe of a patient whose tuberculosis is confined to a single large apical cavity. Without lipiodol bronchography, her copious sputum would be attributed to secretions from the cavity. In the observation of many patients with tuberculous cavitations, one is impressed by the difference in amount of sputum which in some cases is in no degree proportionate to

the size of the vomica. Careful study may show that the variation in amount of sputum may be due to the presence or absence of associated bronchiectasis.

Bronchiectasis, occurring after thoracoplasty, has been recognized by Lilienthal (8), Coryllos (9), Graham and others. Graham (10) states that many of the dilatations found in the basal bronchi after thoracoplasty are really associated bronchiectases which are so frequently present in cases suitable for thoracoplasty and which are accentuated by compression therapy.

Whether the bronchiectasis which is found after thoracoplasty is the remains of a preëxisting dilatation of the bronchi or the result of the fibrosis which ensues after pulmonary collapse is of more than academic interest. First, is a preëxisting bronchiectasis in itself a tuberculous lesion, or is it merely the result of fibrotic changes? Bronchiectasis, occurring postoperatively, must be considered to be nontuberculous, pathologically. Should an attempt be made in the performance of thoracoplasty to collapse associated bronchiectasis? Cabitt, Singer and Graham (11) show radiographs of a case in which preëxisting bronchiectases could not be demonstrated after operation. In view of the well-known fact that bronchiectatic disease is rarely successfully influenced by thoracoplastic collapse, the above result must be considered the exception rather than the rule. Bronchiectasis in the vicinity of the tuberculous lesion is exposed to the collapse procedure, but bronchial dilatations occurring in nontuberculous areas will in no way be affected by a selective partial thoracoplasty.

The presence of nontuberculous bronchiectasis after thoracoplasty has frequently been the cause of an erroneous diagnosis of persistence of active tuberculous disease. The continuance of cough, sputum and râles are misleading factors to the physician who is not acquainted with the possibility of the occurrence of bronchiectasis. Furthermore, haemoptyses frequently occur from dilated bronchi and are the reason for readmissions to sanataria and hospitals in the belief that the bleeding is from a persistent tuberculous lesion. Frequent sputum examinations and lipiodol bronchography must be performed in order to substantiate the diagnosis of healed tuberculosis with residual bronchiectasis.

Uncomplicated bronchial dilatation in itself is of no clinical significance. Dry bronchiectasis may be present in a marked degree without presenting any clinical symptoms. It is only when the bronchial mucosa secretes large amounts of mucopurulent sputum that distressing symptoms

occur. If this secretion can be evacuated easily by the patient, further complications are infrequent. More often the secretion is retained in the bronchial system, becomes foul because of superimposed infection, may be aspirated into healthy parts of the lung and frequently produces bronchopneumonic inflammatory lesions.

Haemoptysis is another frequent and serious complication of bronchiectasis whether the lesion is of the dry or suppurative type. Most frequently, haemorrhages are small in amount, but occasionally they may be severe enough to cause exsanguination. Coryllos (9) reports a death due to haemoptysis from bronchiectatic disease persisting after thoracoplasty. He states that the symptoms from bronchiectasis, following thoracoplasty, may be severe enough to require pneumonectomy.

Amyloidosis is another complication of suppurative bronchiectasis which may eventually lead to a fatal issue. Lastly, it must be remembered that brain abscess frequently occurs during long-standing suppurative disease of the lung.

The treatment of persistent suppurative bronchiectasis following thoracoplasty is quite unsatisfactory. The conservative methods of postural drainage and bronchoscopic irrigation have been tried. Lobectomy or pneumonectomy would appear to be practically impossible because of the marked fibrotic changes in both lung and pleura, the presence of regenerated bone, and the other sequelae of a thoracoplastic operation. X-ray therapy, as has been reported by Berck (12) in bronchiectasis unassociated with tuberculosis, may be given a trial.

Following are abstracts of the histories of two patients in whom thoracoplasty caused a permanent arrest of their pulmonary tuberculosis. Nevertheless, they remained "pulmonary cripples" because of extensive bronchiectasis.

R. H.: no. 13,150, female, admitted to Montefiore Hospital, April 17, 1925, age 38, with five-year history of pulmonary tuberculosis. Pneumothorax had been attempted, and pleural effusion had resulted which was negative on guinea-pig inoculation. X-ray of the chest at this time showed a partial pneumothorax on the right side, with the apex held open by flat adhesions. A large cavity was present in the apical region. Left lung negative. Discharged on December 20, 1925, afebrile, ambulant, and gaining in weight. Remained home for two years, and was readmitted, April 30, 1927, with exacerbation of fever and loss of weight. X-ray was similar to that in 1925 except for reduction in amount of pneumothorax. Patient had two-stage Sauerbruch paravertebral thoracoplasty on the right side in July and August,

FIG. 4

FIG. 5

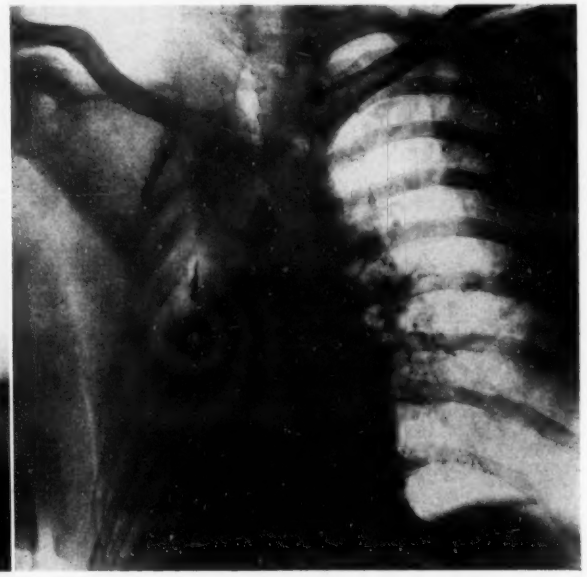

FIG. 6

FIG. 4. R. H., no. 13,150: Marked bronchiectasis following successful thoracoplasty.
FIG. 5. Y. W., no. 18,559: Bronchiectasis following successful thoracoplasty.
FIG. 6. C. S., no. 26,020: Marked bronchiectasis demonstrated 8 weeks after thoracoplasty. (Sputum negative.) Lesion probably present before operation.

1927. A total of eleven ribs was removed. Patient was sent to Montefiore Sanatorium in March, 1928. During 1928 still had occasional haemoptyses, usually before menstrual periods. Last positive sputum occurred on October 18, 1928. All sputa after that date were negative. She remained at home from 1928 to 1930 when she was again admitted to Montefiore Hospital with a history of numerous small haemoptyses and loss of 25 pounds in weight. In one year in the hospital, the patient gained 12 pounds and had frequent haemoptyses. Twelve sputum examinations were negative. The urine contained a slight trace of albumin. The blood urea was normal. She was discharged, 1931, and readmitted in August, 1933, with a history of haemoptyses, loss of weight and 3 ounces of sputum daily. In eight months, the patient regained her weight, although at this time a questionable cavity, which later disappeared, was seen at the left hilum. Twelve sputum and three concentration tests were all negative. She returned home in November, 1934, and felt well until April, 1935, when she was again readmitted with a history of grippe, temperature and loss of weight. Lipiodol bronchography on April 11, 1935, revealed marked bronchiectasis in the right lung (figure 4). Congo-red test showed retention of 40 per cent in the tissues. Urea nitrogen, 22.4 mgm. Urine showed lack of concentration, the highest specific gravity being 1.009. Albumin was 2 plus. A large liver was felt on October 22, 1935. Patient died on October 26, 1935.

Postmortem revealed the right pleural cavity completely obliterated by firm fibrous adhesions. There was extensive calcification of the pleura. This was most marked posteriorly in relation to the old thoracoplasty. Right lung was completely collapsed. On section, there was extensive fibrosis of the upper lobe. No active tuberculosis was made out. Middle and lower lobe were the seat of extensive bronchiectasis. Cut-surface showed only a series of dilated bronchi filled with prune-colored, semiviscid fluid. The intervening lung substance was collapsed. Left lung was voluminous and, except for firm nodules toward the base, felt entirely air-containing. On section, scattered throughout the lower lobe and to a lesser extent in the upper lobe, there were small calcified and chalky nodules representing healed and healing tuberculosis. No active lesions were found anywhere. A calcified hilum lymph node was found on the left. There was marked amyloidosis of liver, spleen and kidneys.

This patient had had a successful thoracoplasty in that it arrested her pulmonary tuberculosis completely. This was evidenced during life by a disappearance of the tuberculous cavity and a consistently negative sputum. Postmortem findings definitely substantiated the clinical evidence. No cavity nor any sign of active tuberculosis could be found in the lungs. In spite of the cure of her tuberculosis, the persistence of

her bronchiectatic disease (which may have been present before operation) was the factor in continuing her invalidism and eventually leading to death from amyloidosis.

Y. W.: no. 18,559, female, was admitted to Montefiore Hospital on September 14, 1929, at age 24. History of onset of pulmonary tuberculosis in 1927. Pneumothorax was induced on left side, 1927, but discontinued because it was ineffectual. On September 18, 1929, X-ray showed bilateral tuberculosis, most marked in upper lobes. Right upper lobe showed moderate number of tubercles with some calcification. Left upper lobe seat of a large cavity, 3½ inches in diameter, and irregular in outline. Blood urea, 13.9 mgm. Patient's general condition improved on rest treatment but pulmonary condition remained the same. Patient complained of eye symptoms and headaches. On March 29, 1930, the fundi presented the picture of a pseudoneuritis. Sinus X-ray was negative. Discharged improved on June 11, 1930.

Readmitted October 9, 1930, with pulmonary condition the same as on discharge. Considered favorable for thoracoplasty. Phrenicectomy done in December, 1930, followed by a two-inch rise in diaphragm. Three-stage thoracoplasty (Sauerbruch) performed in January and February, 1931. In April, 1931, the sputum remained positive and totaled six ounces a day. Patient continued with positive sputum and cavity slowly showed tendency to disappear. Sputum became negative in November, 1933, and has remained persistently negative to this day. Many examinations, including antiformin tests, have been performed.

In February, 1934, 10 per cent of congo-red was retained in tissues in one hour. Urine showed 3-plus albumin. Lipiodol bronchography in December, 1934, showed extensive bronchiectasis of left lower lobe (figure 5). Discharged, January, 1935, to Montefiore Sanatorium where she remained until July, 1935, and then went home. At home, patient again developed poor vision, headaches, anorexia, weakness and copious sputum. She was readmitted to Montefiore Hospital on February 26, 1936. X-ray of chest showed condition similar to previous admission. All sputa, including antiformins, negative. Urine was of low specific gravity, albumin 3-plus, no casts. Sputum averaged six or more ounces daily. Congo-red now shows 25 per cent retained in the tissues. Patient has apparently been cured of tuberculosis to remain an invalid, in part due to bronchiectasis. Complicating factors in this case are an optic neuritis, the exact nature of which has not been determined, and a lesion of the kidneys. Both of these were present before operation. Nevertheless, most of her debilitating symptoms can be traced to her bronchiectatic disease.

This patient presents the clinical picture of a pulmonary tuberculosis cured by thoracoplasty but retaining many symptoms due to a severe

bronchiectasis. The ocular symptoms have been partly responsible for her invalidism, but questioning definitely elicits the information that her copious sputum and chronic pulmonary infection are in a great measure the cause of her debility.

SUMMARY

The purpose in performing thoracoplasty in pulmonary tuberculosis is to obliterate the cavity and render the sputum negative. The complications which may occur after the attainment of a successful result are discussed. Two case histories are presented of patients whose pulmonary tuberculosis was arrested by thoracoplasty but who remained invalided.

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PHRENIC INTERRUPTION COMBINED WITH ARTIFICIAL PNEUMOTHORAX FOR PULMONARY TUBERCULOSIS[1]

FRED R. HARPER

Some physicians believe that phrenic interruption should be used in practically every case of induced pneumothorax either during the course of the pneumothorax or at the time of its abandonment. In this study a group of forty-four cases was selected in which phrenic interruption was done during the course of pneumothorax treatment. All of the cases were patients of the Southern Pacific Railroad Sanatorium, Tucson, Arizona. The patients were all cared for in the same way, each patient remaining at the Sanatorium continuously for at least one year and being rechecked at monthly intervals. This may, therefore, be considered a well-controlled group.

In an effort to determine the effect of phrenic interruption and pneumothorax used in combination, both on the local pulmonary lesion and on the general condition of the patient, the cases have been carefully analyzed with regard to their age, race, weight, symptoms and physical findings of the patients. The X-rays were studied in series to determine the effect of each of the procedures on the local lesion; the rise of the diaphragm was measured, the efficiency of the pneumothorax estimated, the presence and location of pleural adhesions and fluid noted. The amount and pressure of the pneumothorax refills, the temperature, pulse and respiration, the amount and character of the sputum, sedimentation time, and vital capacity were recorded before and after the use of each of the operations and at the time of discharge.

INDICATIONS

Authorities disagree as to which of the two procedures, pneumothorax or phrenic interruption, should precede the other. Bronfin believes that the simplicity, effectiveness and flexibility of pneumothorax make it the method of choice, and that it should be used before any other method is attempted. Head, Schlack and Marx contend that phrenic

[1] From the Thomas-Davis Clinic and the Southern Pacific Railroad Sanatorium, Tucson, Arizona.

interruption does not favor the formation of adhesions, and that the procedure should be used before pneumothorax is attempted. Nehil and Alexander agree that the phrenic operation does not cause pleural adhesions, and present the additional argument that many lesions will show such marked improvement or healing that subsequent pneumothorax is unnecessary. In 16 of this series of 44 cases phrenic interruption was employed first, while in 28 cases pneumothorax was used as the first treatment.

TYPE OF CASES

The National Tuberculosis Association has classified cases of tuberculosis as minimal, moderately advanced and far advanced. In this series 24 cases were far advanced, 16 moderately advanced, 3 minimal, and 1 case had pneumonoconiosis with tuberculosis superimposed. Thirty-one cases had bilateral lesions and 13 cases had unilateral lesions. Of the 31 cases with bilateral lesions, 9 cases had bilateral cavitation. The sputum in 37 of the 44 cases was positive on entrance.

This group includes 4 women and 40 men. The average age was 38 years; the oldest was aged 56 years and the youngest 23 years. Patients past middle life have always been considered as poor risks for any type of collapse therapy. Bendove states that, in patients 50 years of age or more, one must be very cautious in performing pneumothorax treatments. In this series 5 patients were more than 50 years of age; 4 were clinically cured, and 1 was improved. While it is true that one must proceed cautiously in older patients, collapse therapy is not necessarily contraindicated.

O'Brien mentions that, because of their lack of resistance, surgical procedures are not as effective in the Mexican, Negro and Indian as in other races. He points out that in this type of patient the so-called "spreads" occur more often. It is probably true that in these races the exudative type of lesion is more commonly encountered. If, however, the cases are carefully selected, there is no reason for not using collapse therapy in these patients. In this series there were 7 Mexicans, 1 Indian and 1 Negro. Of the Mexicans, 3 were clinically cured, 2 improved and 2 died of miliary spread. The Indian was much improved and the Negro cured.

CAVITIES

Pollock and Forsee found that when cavities remain patent after a period of moderate pulmonary collapse by pneumothorax, or fail to

become obliterated after a satisfactory period by diaphragmatic paralysis, the combination of the two procedures will often result in rapid obliteration of the excavation.

The cases were divided into two groups according to the location of the cavity and the effectiveness of the type of therapy used. The first group includes cases with unilateral apical cavities; the second group includes basal cavities, some of which had bilateral cavitation.

In 19 cases with unilateral apical cavitation, pneumothorax was used first. In 8 cases pneumothorax reduced the size of the cavity but did not close it. After the addition of phrenic interruption the cavities completely closed and the lesions healed. In 6 cases the pneumothorax was sufficient apparently to close the cavity but, because the lesion had not completely healed or because the sputum was still positive, phrenic interruption was added, which completed the healing of the lesion. In 5 cases pneumothorax reduced the size of the cavity and phrenic interruption was of further benefit, but the combination of the two procedures was not sufficient to close the cavity. It was necessary to resort to further collapse procedures.

There were 9 cases with unilateral apical cavitation in which phrenic interruption preceded pneumothorax. In 3 of these cases the cavity was reduced following the phrenic operation and the addition of pneumothorax closed the cavity. In one case in which there were multiple small cavities, the phrenic operation apparently closed the cavities, but it was necessary to add pneumothorax to bring about complete healing of the lesions. In 2 cases the phrenic operation reduced the size of the cavity and the addition of pneumothorax helped further to reduce the cavity's size but did not close it. Three of the cases deserve special consideration. In these three cases there was a small apical noncavernous lesion before the phrenic interruption was done. In from one to three months after the phrenic interruption, definite cavitation appeared at the site of the infiltrated lesion. When the cavity appeared, pneumothorax was added which was sufficient to bring about complete closure.

BASAL CAVITIES

Slavin believes that cavities situated in the lower lobe show more initial collapse and become obliterated more rapidly following phrenic paralysis than do upper-lobe cavities. On the other hand, in Nehil's and Alexander's series only 2 of the 7 basal cavities were closed by phrenic paralysis; of the remaining 5 cases, 4 were suitable for some supplementary collapse-therapy measure.

Seven cases in this series had basal cavities. In 5 cases the basal cavities were associated with apical cavities in the opposite lung. In 4 cases the basal cavities were more than 4 cm. in diameter. In the other 3, they were between 2 and 2.5 cm. in diameter. In 5 cases pneumothorax was given first and was successful in reducing the size of the cavity; but the cavity did not close until phrenic interruption was added. In one case the pneumothorax closed the cavity and phrenic paralysis was added for additional precaution. In one case the cavity apparently was closed with phrenic interruption when pneumothorax was added.

BILATERAL CAVITIES

Bilateral collapse therapy is justifiable if the cases are carefully selected. It is always advisable if possible to begin with the more extensively diseased side. Davies feels that under no circumstances should the second lung be reduced to less than two-thirds of its volume. Alexander, although advising against it, considers bilateral permanent phrenic paralysis, or simultaneous temporary paralysis, to be perfectly compatible with life, provided the vital capacity is sufficient, so that asphyxia will not result when the function of both hemidiaphragms is abolished. In this series, 9 cases had bilateral cavitation. In 4 cases the combination of phrenic interruption and pneumothorax was used on the side of the more advanced lesions. In 3 of these cases the opposite side cleared entirely, and in the other case there was improvement. In 2 cases, alternating pneumothorax was used with phrenic interruption on the more advanced side. One of these cases was entirely cured and the other case died of spontaneous pneumothorax. In 2 cases bilateral simultaneous pneumothorax was used and phrenic interruption was done on the more advanced side. In one of these cases a good result was obtained, while the other patient was dyspnoeic at times and had occasional haemoptysis during his stay in the Sanatorium. In 1 case, phrenic interruption was used on one side and pneumothorax on the other side with satisfactory results.

PHRENIC INTERRUPTION

Nehil and Alexander state that their best results following phrenic paralysis have been in limited lesions that were relatively fresh, and that contained fibrous tissue that was young enough to be still capable of considerable contraction. Their least satisfactory results were in extensive fibrotic lesions with large stiff-walled cavities.

In most instances temporary phrenic interruption by crushing is preferred to permanent exairesis, because of the desirability of having a return of the diaphragmatic function when the purpose of its paralysis has been accomplished. In this series, 33 cases had temporary phrenic interruption, while 11 cases had permanent paralysis.

Whether or not the amount of the rise of the diaphragm is in direct proportion to the results obtained following phrenic interruption is a disputed question. Slavin says that the complete closure of responsive cavities depends on their size and on the condition of the opposite lung, and is not controlled by the amount of elevation of the paralyzed diaphragm. Graham, Singer and Ballon believe that a marked rise of the diaphragm following phrenic paralysis does not mean that the improvement that follows will be striking. On the other hand, Matson thinks that the best results are always associated with a marked rise of the diaphragm.

In this series, in 18 of the cases the diaphragm rose 5 cm. or more. Out of this number, 13 had good results, as evidenced by closure of the cavity and negative sputum, while only 5 cases had unsatisfactory results. Of 16 cases with less than a 5-cm. rise of the diaphragm, 10 could be considered as having obtained good results, while in 5 cases the results from the operation were not entirely satisfactory. In one case the expectancy was fulfilled, but the cavity was so large that thoracoplasty was necessary later. However, it must be remembered that all of these cases were getting pneumothorax and that in some instances a good rise of the diaphragm was prevented by the pneumothorax.

Pollock and Forsee state that gas between the pulmonary base and the diaphragm hinders pulmonary collapse, in that the diaphragm fails to ascend into the hemithorax subsequent to the hemidiaphragmatic paralysis. In the 44 cases under consideration, there were only 13 cases in which the base of the lung was definitely adherent to the diaphragm. In spite of the smallness of my series, it would seem that adhesions to the diaphragm were not an essential factor in obtaining good results when phrenic interruption is used in conjunction with pneumothorax.

PNEUMOTHORAX

Trudeau thinks that fewer, smaller, and quickly absorbed pleural effusions occur when phrenic paralysis is used in conjunction with pneumothorax. Alexander believes that the influence of phrenic paralysis in reducing the incidence of effusion is not direct, but that it does so

only in so far as it assists in rendering inactive the subcortical tuberculous lesions. All of the cases in this series were kept on negative, or very slightly positive, pressure. Fifteen of the cases with slightly positive pressure developed fluid, while 9 cases under similar pressures did not develop fluid. Five of the cases which were on negative pressure developed fluid, while 15 that were on negative pressure did not develop fluid. Of the 20 cases in which fluid developed, 16 cases cleared up spontaneously, and 4 cases developed empyema. Of these 4 cases, one was clinically cured, one improved, one improved following thoracoplasty and one died.

In all of the cases there was only partial collapse of the lung obtained with pneumothorax. The estimated collapse varied from 30 to 85 per cent. Disregarding the amount of collapse, an effort was made to determine whether or not the pneumothorax could be considered successful in relaxing the diseased portion of the lung. In 26 cases the pneumothorax partially relaxed the diseased lung. Eleven of these cases were clinically cured, 14 definitely improved, and one died. Eighteen cases were classed as unsuccessful as far as any suppression of the cavity was concerned. Four of these cases were cured, 7 improved, and 2 cases had thoracoplasty with good results. Four of the patients died.

Frank and Miller state that in those cases in which pneumothorax must be kept up indefinitely, phrenic paralysis adds a margin of safety and lessens the number of refills. Decker, on the other hand, does not believe that the use of phrenic interruption in conjunction with pneumothorax either diminishes the incidence of pleural effusion or lessens the frequency of refills. Of my 20 patients who were receiving regular pneumothorax refills at the time the phrenic operation was added, the time between refills was lengthened in 14.

SPUTUM

In my series, 37 patients had positive sputum on entrance. Thirty-three of these became negative after the combined treatment. In order to determine the effectiveness of phrenic paralysis and pneumothorax individually, the cases in which pneumothorax was used first and those in which phrenic interruption was instituted first were analyzed separately. In 14 out of 22 cases the sputum became negative after the pneumothorax before the phrenic was added. In 8 cases, the sputum did not become negative until after the phrenic operation was added to the artificial pneumothorax. Five cases had a negative sputum when treatment was begun and one case died of spontaneous pneumothorax.

Of the group in which phrenic interruption was the first procedure, the sputum became negative after this operation in 4 cases; the sputum did not become negative until the pneumothorax was added to the phrenic in 6 cases; the sputum remained positive in 3 cases; the sputum was negative before and after treatment in 4 cases.

The question of the amount of sputum was also analyzed. Of the cases in which pneumothorax was used first, in 6 cases the sputum was reduced following pneumothorax, and stopped with the addition of phrenic paralysis; in 7 cases the sputum was reduced following pneumothorax and further reduced following phrenic paralysis; in 3 cases the sputum disappeared entirely following the pneumothorax. There were 4 cases in which the pneumothorax did not reduce the sputum, but with the addition of phrenic interruption the sputum was reduced. In 3 cases pneumothorax reduced the sputum and there was no further reduction following phrenic interruption. In 4 cases the amount of sputum was not reduced with the combined procedures, but became negative. When phrenic interruption was used first, the sputum became reduced in 10 cases and the addition of pneumothorax further reduced it. In 3 cases the phrenic operation reduced the sputum which disappeared with the addition of the pneumothorax. In one case the phrenic paralysis alone stopped the sputum. In one case the sputum was unchanged, and one case did not have any sputum.

GENERAL CONDITION OF THE PATIENT

Matson says that following exairesis of the phrenic nerve, there is reduction of fever and diminution of expectoration, and coincidently a corresponding improvement in the general condition of the patient. The appetite improves, the weight increases, the fatigue subsides, the secondary anaemia disappears, and the patient looks and feels much better. In my group of cases a marked improvement in the patient's general condition was the rule. The average gain in weight was 26 pounds. There were 33 patients who gained weight, 6 who lost weight, 2 in whom the weight was unchanged, and 3 patients died in the hospital. The white blood count was reduced in 28 cases, and the red blood count was increased in 41 cases at the time of discharge. The sedimentation time in 41 of the 44 cases was lower at the time of discharge than on entrance. In 21 cases the sedimentation time dropped to normal. There was no marked rise in sedimentation time after the institution of either pneumothorax or phrenic interruption.

In an experimental study on dogs, Lemon found that phrenic interrup-

tion brings about no impairment in the subject's functions in general or of the respiratory functions in particular. Alexander, however, considers vital capacity important, and will not induce a phrenic paralysis on any patient who is even slightly dyspnoeic or cyanotic in bed or during moderate exertion. My cases were carefully selected and only cases with fairly good vital capacity treated. There were 4 cases in which the vital capacity was less than 1,800 cc. In all the other cases, the vital capacity was from 2,000 to 4,900 cc. In 16 cases the respiratory rate was lower on dismissal than on admission, while in 19 cases the respiratory rate in bed was unchanged and in 5 cases it was higher. There were no patients who were dyspnoeic following either or both procedures with the exception of 2 cases in which spontaneous pneumothorax occurred.

In 3 cases there were severe reactions with elevated temperature and pulse after pneumothorax refills; 2 of these patients died. None of the other cases had any marked changes in either the temperature or pulse-rate after either the pneumothorax or phrenic interruption.

RESULTS

There were 17 patients that were apparently cured; 4 patients were considered as having arrested tuberculosis while the tuberculosis in 14 patients was classified as apparently arrested, quiescent or improved because the time interval was not sufficient to put them into the apparently cured or arrested groups. Six cases had further collapse procedures. Three cases died from miliary spread or spontaneous pneumothorax.

SUMMARY

A group of predominantly severe cases of pulmonary tuberculosis in which phrenic interruption was used in conjunction with pneumothorax was carefully analyzed. It was found that the combination of the two procedures was effective in closing 80 per cent of the cavities that had failed to close when only one of the procedures was used. Also, the two procedures used together were more effective than either used singly in reducing the amount of sputum and caused it to become negative for tubercle bacilli in 89 per cent of the cases. A group of cases of pulmonary tuberculosis with bilateral cavitation was successfully treated by using these two procedures in various combinations; the bilateral cavities became completely closed in 77 per cent of this group. Phrenic interruption added to pneumothorax was effective in decreasing the incidence

and severity of pleural effusion and increased the interval between pneumothorax refills. The two procedures did not produce any detrimental effects on the general condition of the patient and were used in combination without any appreciable added risk. The final results following the combined use of phrenic interruption and pneumothorax have been so gratifying as to indicate the use of the second operation in a considerable group of patients in which the operation first used proves to be incompletely effective.

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SELECTIVE COLLAPSE IN ARTIFICIAL PNEUMOTHORAX

A Consideration of Its Development[1]

RICHARD T. ELLISON

With the increased use of artificial pneumothorax and a growing tendency toward the use of low pressures, a better understanding of the mechanism of the development of so-called selective collapse becomes of greater and greater importance. Since the introduction of hypotensive pneumothorax in 1912, and the recognition of a selective factor in the degree of collapse of different parts of the lung, there have been many theories advanced as to the manner in which the observed phenomena have developed. None of these theories have been entirely satisfactory. The only excuse for again opening this subject is the hope that by reviewing some of the older theories in the light of recent developments in physiology we may come to a more reasonable comprehension of the *modus operandi* of selective collapse.

First, it must be thoroughly appreciated that the development or production of selective collapse is entirely beyond the control of the operator. If those physical forces and principles of physiology which lead to the collapse of pulmonary tissues are operative equally in all parts of the lung, there can be no selective collapse. We cannot say in any particular patient, "We will induce a selective collapse in this case;" for, unless the factors permitting such a selective collapse are "right," it is beyond the power of the operator to produce it. All we can say is "If things are 'right,' we will not push our pneumothorax beyond the stage of selective collapse;" for every selective collapse can be extended to a complete collapse and this is within the power of the operator. I am assuming here, and in all of the discussion to follow, that the pleural space is free and that there are no adhesions to make such a collapse a physical impossibility.

The very term "selective collapse" takes cognizance of a difference in function in various parts of the lung. The existence of such a difference

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is an absolute necessity for the production of selective collapse. The cause of this difference is some pathological process that leads to an alteration in the normal physiology of the area of lung tissue concerned, but this pathological process need not be the same in all parts of the lung. Usually we are dealing with a tuberculous process in the upper lobe of a lung with no involvement in the lower lobe. Such a situation would lead to a selective collapse of the upper lobe when artificial pneumothorax is instituted. But if the lower lobe, instead of being healthy, were the seat of a chronic nontuberculous bronchosinusitis, this might alter the physiology of that lobe to an extent similar to the lesion in the upper lobe, and no selective collapse would be possible.

During the past few years, while inducing artificial pneumothorax on a large number of patients, I have noted that selective collapse does not always develop in the same way. Cases can be divided into two distinct groups, differing sharply in the time and the mechanism of development. First, we have those cases in which the selective feature of collapse develops at once on the introduction of air into the pleural cavity: this I have called *Immediate Selective Collapse.* Second, there are those cases in which the selective collapse does not develop until some time after the introduction of air into the pleural cavity: this I have called *Delayed Selective Collapse.*

IMMEDIATE SELECTIVE COLLAPSE

Before considering the mechanism of immediate selective collapse, let us review certain phases of pathological physiology that have a direct bearing on this problem. Fibrosis and/or atelectasis of one lobe of a lung leads to a shrinkage and loss of volume in that lobe. This loss of volume must be replaced, and there are four possible ways by which it can be done. Any one of these compensatory mechanisms may operate by itself or in combination with any one or all of the other three. First, the chest wall may move inward; second, the mediastinum may swing toward the involved area; third, the diaphragm may rise and reduce the total volume of the hemithorax; and, fourth, the uninvolved lung tissue, the other healthy lobe, may enlarge by the development of a compensatory emphysema. All these changes are the result of a local reduction in pressure within the hemithorax due to the loss of volume. The surrounding structures on all sides are dislocated from their normal positions at rest toward the area of lessened pressure and maintained there against their own elastic recoil. The underlying principles of physics

and their application to this problem have recently been considered by Andrus (1). Elasticity of the lung plays a negligible part in the production of these changes. The major lines of force generated by the elastic tissue of the lung lie in the direction of the bronchovascular tree, about which most of the elastic tissue is situated, whereas the lines of force generated by fibrosis converge on a point of equilibrium in the centre of the involved area. Also, the magnitude of these latter forces far overshadows that of the elastic tension.

Another point that must be appreciated is that even in normal chests the stress between the visceral pleura and the chest-wall differs at different points (2). This is due to the pull of gravity on the lung structures. The difference in stress is not great, but it is sufficient to influence the movement of gas within the pleural space. In the upright position this stress is greatest over the apex and least at the base; in the usual position for induction of pneumothorax it is greatest in the mid-axillary region. In pathological conditions with fibrosis and/or atelectasis, the magnitude of the stress is greatly increased over the diseased areas, and readily overcomes and replaces the shifting values due to gravity. Once the coaptation of the two layers of the pleura has been released by the introduction of air, the pressure within the pleural space becomes uniform throughout, and the localization of the air depends on the volume of the underlying lobes and the effect of gravity on them.

What is the application of these facts of physics and physiology to the development of immediate selective collapse? In most cases of pulmonary tuberculosis a certain amount of fibrosis and/or atelectasis has developed in the diseased area before the induction of artificial pneumothorax; this is especially so in the productive and fibrotic types of the disease. This fibrosis and/or atelectasis results in a loss of volume of the diseased lobe, and in an increased stress between it and the surrounding structures, so that the stage is set for the immediate development of selective collapse, once the coaptation of the pleura has been relieved by the introduction of an expansile substance such as air. We have then a lobe, shrunken by fibrosis and/or atelectasis, which is exerting traction on the perilobar structures. The force developed by this contraction far exceeds that of the elastic recoil of the lung, as is evidenced by the displacement of the surrounding structures from their normal positions at rest. The force causing this displacement is counterbalanced by an equal force tending to restore the surrounding structures to their normal position, were it not for the nonexpansile layer of fluid

which holds the two layers of the pleura together. The lobe, reduced in volume by fibrosis and/or atelectasis, is in a static state and is not amenable to rapid changes in size. It does contract slightly when the counterforce of the perilobar structures is released, but beyond this it is fixed as regards both increase and decrease in size except for the gradual advance of the fibrotic process. If now we introduce an expansible gas such as air into the pleural space, the perilobar structures spring back to their normal positions at the expense of a reduction in pressure of the air, until its volume is sufficient to compensate for the volume lost by shrinkage of the diseased lobe. Dumarest and Lefevre (3) have recently discussed these principles.

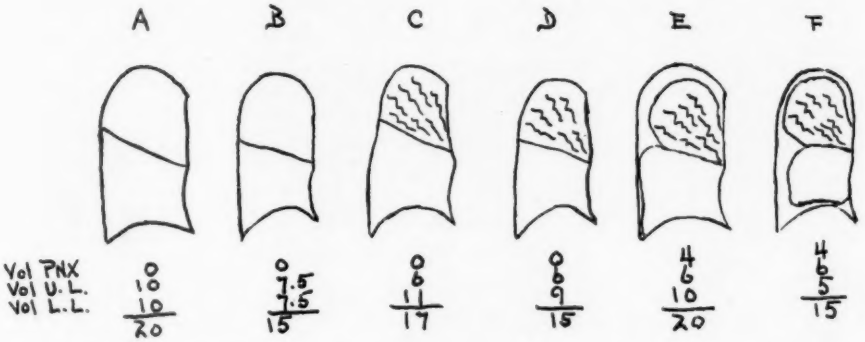

FIG. 1. Diagrammatic schema of a hemithorax, showing the development of immediate slective collapse when one lobe is the seat of fibrosis and/or atelectasis.

Figure 1 is an attempt to show schematically the development of this type of collapse. *A* represents the inspiratory phase of a normal hemithorax which contains 20 volumes, divided for our purpose equally into two lobes. The volumes used in this schema are entirely arbitrary, and are not to be correlated directly with clinical material. *B* represents the expiratory phase of the same hemithorax, and we see that there has been a reduction of 5 volumes, this loss being divided equally between the two lobes. *C* represents the inspiratory phase of a hemithorax in which fibrosis and/or atelectasis has caused a loss of 4 volumes in the upper lobe. This loss of volume has been compensated for to the same degree by each of the four mechanisms mentioned above. We see that the chest-wall has been drawn inward, that the mediastinum has been drawn toward the lesion, that the diaphragm is raised, and that the healthy lobe has become emphysematous. This results in a reduction of only 3 volumes

in the total capacity of the hemithorax because the lower lobe now contains 11 volumes. In *D* we see the expiratory phase of this condition. Here the loss of volume during expiration has been taken up chiefly by the mechanisms of compensation. The involved lobe has not been further reduced in size, and the healthy lobe has only changed by 2 volumes from its capacity during inspiration. This situation is frequently seen clinically in restriction of the excursion of the entire hemithorax in which only one lobe is diseased. At *E* we see the inspiratory phase of the hemithorax immediately after the induction of artificial pneumothorax.

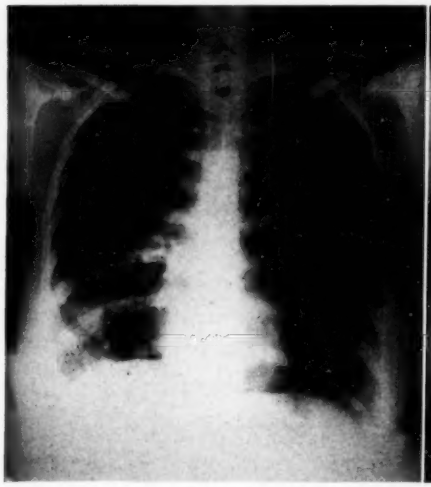

FIG. 2

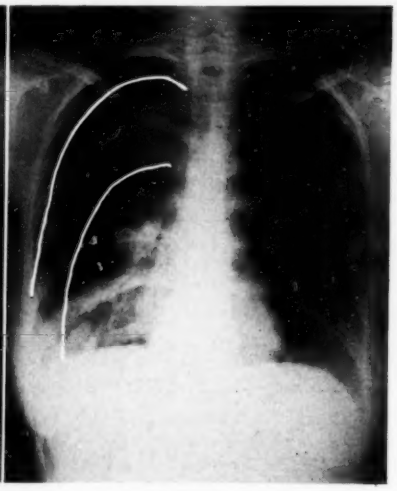

FIG. 3

FIG. 2. Fibroulcerative lesion in right lower lobe, showing some fibrosis and/or atelectasis. Note slight elevation of right diaphragm.

FIG. 3. Same chest immediately after induction of artificial pneumothorax. Note selective collapse of right lower lobe and normal position of diaphragm.

We see that all of the compensatory mechanisms have returned to their normal state. The 4 volumes of air introduced have immediately become localized over the diseased area, and its loss of volume is now compensated for by the pneumothorax. *F* is the expiratory phase, and shows that loss of volume here has been accomplished by a reduction in the capacity of the lower lobe. It should be noted especially that at this stage the volume change of the lower lobe is twice that under normal conditions. This also is readily demonstrable on fluoroscopic observation of patients with this type of collapse, in whom the hyperfunctioning healthy lobe readily catches the attention. From this point on, further

development of selective collapse depends on a continued loss of volume in the upper lobe from increasing fibrosis and/or atelectasis. If this does not occur, further collapse of the diseased lobe can only be accomplished by abandoning the selective feature and pushing the pneumothorax to a complete collapse.

Figures 2 and 3 show roentgenograms illustrative of this type of collapse taken before and immediately after the induction of artificial pneumothorax. In the first roentgenogram it is obvious that we are dealing with a tuberculous lesion of the lower lobe, in which a certain amount of fibrosis and/or atelectasis has already occurred. This is evidenced by a slight rise in the right diaphragm. In the second roentgenogram we see that the air has immediately become localized over the diseased area and we have a definite, well-established selective collapse. Also, the compensatory elevation of the diaphragm has been released by the induction of pneumothorax and the diaphragm has assumed a normal position. This case was selected for illustration because the lesion was in the lower lobe and demonstrates that the selective feature is not the result of gravity.

DELAYED SELECTIVE COLLAPSE

We now come to by far the less frequent mode of onset of selective collapse, but the one which has stimulated the greatest amount of discussion, and concerning the development of which there have been advanced the greatest number of conflicting theories. Most of these theories have been based on a consideration of the elasticity of the lung, and most of them have predicated an increased elasticity in the diseased portion of the lung.

Let us consider first, therefore, this question of pulmonary elasticity. The elastic fibres of the lung form a highly specialized type of tissue, which has been fully developed by the time adult life has been reached. The fibres are arranged as a loose mesh throughout the substance of the lung, but are gathered together into a more definite structure in the walls of the bronchi and their accompanying blood-vessels. Here they exert definite lines of force operating in the direction of the bronchovascular tree. They exert a definite force in all phases of respiration, because after the full expansion of the lung they are never entirely relaxed, even in expiration. With one end of this elastic tension fixed at the hilum, the practical effect on the lung is to produce an approximation of the pleura to the hilum, or, in other words, a collapse of the lung.

Inspiration increases the elastic tension along these lines of force by separating the points of attachment, but I know of no evidence to support the contention that the amount of elastic tissue in the lung can be increased. Least of all does it seem logical that such an increase could be brought about by inducing a disease process in the lung. If then we cannot increase the amount of elastic tissue in the lung or separate the points of attachment beyond definite limits, we cannot offer increased elasticity as the reason for selective collapse.

Let us review for a moment some of the explanations for the development of selective collapse that have been advanced in the past. One of the first to interest himself in this question was Morgan (4), in 1913. He believed that elastic tension was lost in consolidated areas, and therefore the elastic tension in other parts of the axis from hilum to periphery was increased. He injected agar into rabbits' lungs in a pressure-chamber, and noted that, when the lung collapsed, the area of agar infiltration bulged above the surrounding surface and when the lung expanded the position of the infiltration was marked by a depression. Following this there was no further effort to explain the mechanism of selective collapse until about 1922. Then Gwerder (5), in a consideration of this problem, stated:

> During the induction of a low-tension pneumothorax, particularly in the cases of consolidation, for which it is indicated, it often happens that the gas becomes spontaneously localized over the affected area, i.e.—over the area of least resistance. The lung is inelastic over this part and the range of respiratory movement less; hence the fuller movement of the normal part drives the gas toward it (the affected area).

This same year Barlow and Thompson (6) devoted less than four pages of a two hundred and fifty page monograph on pneumothorax to selective collapse. In a general discussion they pointed out that in certain conditions the diseased part of the lung contracts more readily than the normal part, and also is more difficult to reinflate. Again, Barlow and Kramer (7), in 1922, pointed out that selective collapse was the result of impairment of expansibility in the diseased portion of the lung and not the result of gravity.

Barlow (8), in 1923, summarized these observations and deductions as follows:

> Selective collapse is a term which we have applied to the collapse of diseased or irritated lung tissue following a partial pneumothorax, in virtue of the property

of such tissue to remain contracted after expiration, the respiratory movement being taken up by the unaffected portion of the lung. This contraction is increased with each respiration until the elastic tension of the expanded portion overcomes the tendency of the diseased or irritated portion to contract. If air is admitted into the free pleural cavity it will come to rest over the lesion on account of the greater tendency of this portion of the lung to contract, and will permit unrestricted action of the principle of selective collapse. Selective collapse of such a lesion is usually nearly complete in one to three days but there is often a slight increase of the collapse for several weeks.

Here then we have recognition of the fact that infiltration of the lung affects its elasticity, that these changes affect distensibility to a greater degree than contractility, and that collapse of such a lesion does not occur immediately on the introduction of air into the pleural cavity, but slowly, over a period of time. In 1930 (9), and again in 1934 (10), Cutler conjured up an "expansile pulmonic force" to account for selective collapse. He said:

The diseased area is kept collapsed partly, as has been observed, by its own inelasticity and also by the pressure of the gas forced repeatedly toward this area by the expansile action of the healthy part of the treated lung (5). This motion imparted to the gas by the elastic lung tissue during respiration may be called expansile pulmonic force. The expansile pulmonic force, therefore, results from the expansion of the unaffected part of the treated lung on inspiration.

It is, however, impossible for such a hypothetical positive force, which cannot exceed atmospheric pressure, to operate in a cavity where the pressure is constantly less than atmospheric, and to compress a part of the lung which is also exposed to atmospheric pressure.

Matson (11) referred to the "collapse capacity" of the diseased pulmonary tissue, but this is merely a phrase which offers nothing in the way of explanation of the condition.

It is Van Allen (12) who has recently made the most serious attempt to explain the part played by pulmonary elasticity in the development of selective collapse. In summarizing his article he says in part:

Differentiation is made between the deflation of the diseased tissues which occurs immediately and is probably due to increased elastic tone of the lung, and that which occurs gradually and is due to formation and contraction of scar tissue. The increased elastic tension of the lung, in the first type, is believed to be due largely to thickening of the pulmonary septums and mem-

branes from vascular congestion and interstitial deposit of inflammatory fluids and cells.

Here Van Allen differentiates between immediate selective collapse and delayed selective collapse, but he has attributed the latter to causes which, as I have shown above, bring about immediate collapse; and he has attributed an increased elastic tension to factors that I will subsequently show result in an increased inertia and a decrease in elastic tension.

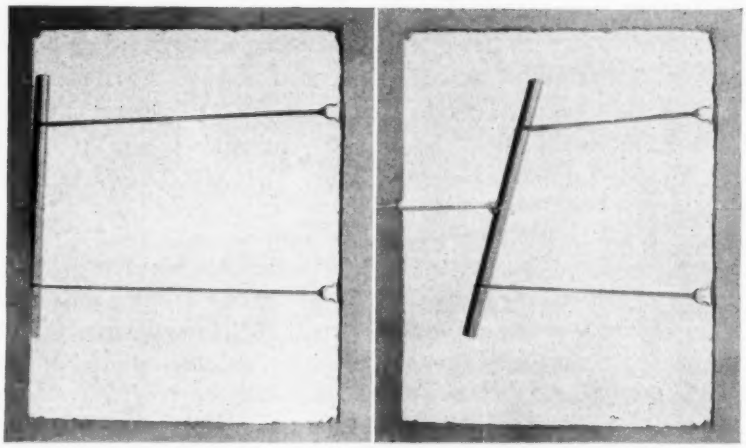

FIG. 4 FIG. 5

FIG. 4. Working model, representing a hemithorax demonstrating the effect of pulmonary elasticity in the production of selective collapse. The elasticity of the upper lobe is here represented as twice that of the lower lobe.

FIG. 5. Same as fig. 4 after separation of "pleural" surfaces. Note greater collapse of upper lobe.

Figure 4 shows a photograph of a simple reconstruction of the model used by Van Allen. This reconstruction is a cardboard frame, which represents the structures surrounding the pleural cavity. To the mediastinal side are attached, by stickers, rubber bands taken from the same lot, and therefore being as nearly similar as possible. These represent the tension of the elastic tissue of the upper and lower lobes, with one end fixed at the hilum. The rubber bands are brought out at right angles to the mediastinal surface and looped over a wooden bar which is held against the costal side of the frame by a cord attached to the bar at a point midway between the rubber bands. This bar represents the pleural surface of the lobes and the cord the force exerted by the coapta-

tion of the pleura. The elastic tension of the upper lobe is here represented by two rubber bands and that of the lower lobe by one. Van

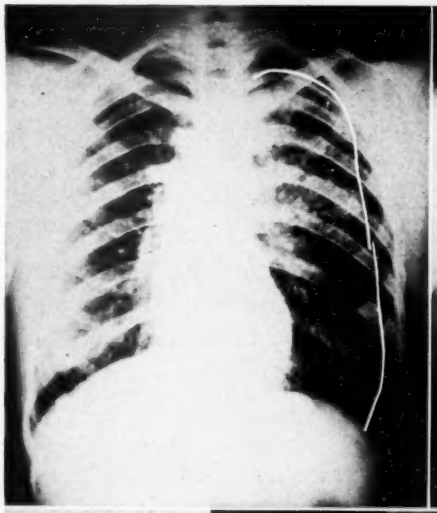

FIG. 6

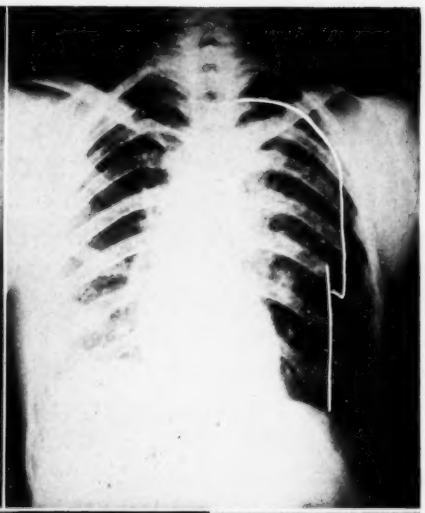

FIG. 7

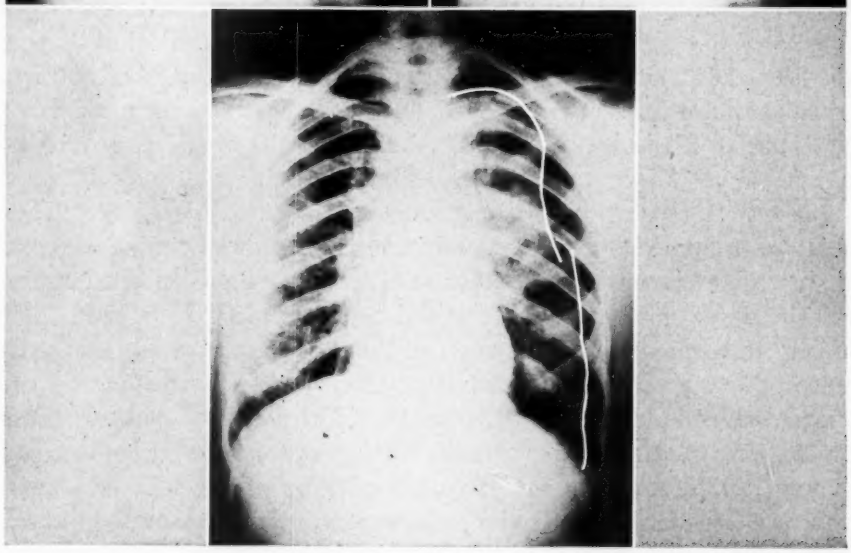

FIG. 8

FIG. 6. Inspiratory phase taken immediately after initial instillation of air. Comparable to fig. 11, *C*.

FIG. 7. Expiratory phase following fig. 6. Comparable to fig. 11, *D*.

FIG. 8. Inspiratory phase of same chest taken six days later. Comparable to fig. 11, *E*.

Allen says, "The bands are the same length when completely relaxed but the upper band has the greater thickness and elastic tension, which cir-

cumstances imitate the pulmonary lobes when the upper one is tuberculous." In figure 5 the cord has been lengthened to represent the separation of the pleural surfaces by air. We see that the greater amount of elastic tension in the upper lobe has caused a greater displacement of the bar over that lobe,—in other words, a selective collapse.

Such a state of affairs, however, cannot exist in the lung. I have tried above to stress the point that the amount of elastic tissue in the lung does not increase. Van Allen has not increased the tension of a normal amount of elastic tissue by further stretching but has arbitrarily increased the amount of elastic tissue. Nobody before has intimated that the tuberculous lung contains many times as much elastic tissue as the normal lung. Yet that is what the above explanation means,—an hypertrophy of the elastic tissue of the lung brought about by tuberculosis: a theory obviously not supported by fact.

If selective collapse is not caused by an increase in elastic tension due to increasing the amount of elastic tissue, may it be caused by a loss of tension from loss of elastic tissue? To illustrate this let us consider the upper lobe in figure 4 to be the normal one and the elastic tissue of the lower lobe to have been reduced by one-half through pathological change. On introducing air, as in figure 5, we see that the healthy lobe contracts more than the diseased one,—the latter is emphysematous as compared with the healthy lobe. This is the direct opposite of selective collapse.

Several years ago, in considering this question of selective collapse, I decided to X-ray patients with a bronchopneumonic type of tuberculous infiltration immediately after the first instillation of air. Figures 6 and 7 are reproductions of roentgenograms taken in inspiration and expiration within a few minutes of the initial pneumothorax treatment. For clarity in reproduction the margin of the visceral pleura has been outlined. We see here that, in contrast to the picture in figures 2 and 3, the diseased lobe is less collapsed than the healthy lobe, and the latter is functioning to a far greater extent with respiration. In figure 8 we see, however, that within a few days the position of the lobes has been reversed and we have a selective collapse of the diseased lobe.

How can we account for this situation? It is evident that increased elasticity is not playing a part here because it is obviously more difficult to compress the diseased lobe. What, then, is interfering with the normal elasticity of the upper lobe? In this type of early tuberculous disease we have a bronchopneumonic infiltration instead of a fibrosis and/or atelectasis, which, as we saw above, produced immediate selec-

tive collapse. Here there is an outpouring into the tissue-spaces of serum, fibrin and cellular elements, that stiffen the tissues and hold them in a distended position. The effect on the elastic tissue contained in these infiltrated areas is to prevent it from contracting. The total elastic recoil along the lines of force through the infiltrated areas is reduced. As we saw before in the model, the diseased lobe is emphysematous with respect to the healthy lobe; but this is not all of the story, because in figure 8 we see that in a few days a selective collapse of the infiltrated lobe has occurred. The answer lies in a consideration of differences in function between the lobes. The infiltration of the diseased

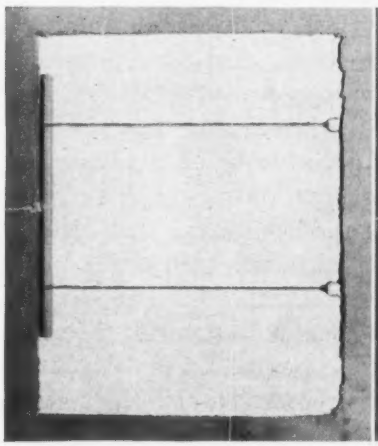

FIG. 9

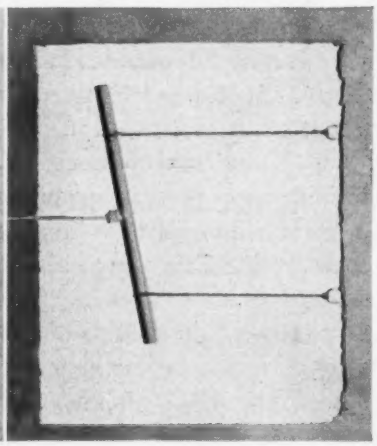

FIG. 10

FIG. 9. Model of hemithorax in which elasticity of both lobes is the same, but to the upper elastic spots of glue have been applied.

FIG. 10. Same model as fig. 10 after separation of "pleural" surfaces. Note selective collapse of lower or normal lobe.

lobe has impaired its function; it has made it difficult for it to contract and even more difficult for it to reëxpand; it has increased its inertia.

Let us return again to the model of Van Allen for an explanation. Figure 9 shows the same model as before, except that this time the elasticity of both lobes is the same and is represented by one elastic band. Here we have the condition before pneumothorax. Both lobes are the same, but to the upper elastic I have added spots of glue to simulate pulmonary infiltration. The glue does not continuously coat the rubber band, but leaves stretches of uninfluenced elasticity between the points of application. In figure 10 we see the effect of this procedure on the

elasticity of that lobe; it retracts less than the healthy lobe and is similar to the roentgenogram, figure 7. If the glue is applied while the elastic bands are partly relaxed, we will find that on pulling on the cord it is more difficult to expand the upper lobe. These models however differ in a very essential respect from the actual conditions in the chest. The model is static, whereas the thoracic cage and its contained viscera are dynamic and subject to volume changes. During expiration there is a loss of volume in the hemithorax. The air is normally expelled from all parts of the lung through the trachea in an evenly distributed manner. In pneumothorax, however, a part of the contents of the hemithorax is not in communication with the trachea but is trapped in the pleura. When the hemithorax is reduced in volume by expiration, this entrapped air, while it may be influenced somewhat by changes in pressure, maintains essentially its original volume and therefore occupies a much greater percentage of the entire volume of the hemithorax than before. Also, while the intrapleural pressure is negative in both phases of quiet respiration in low-pressure pneumothorax, during cough there may be such a great reduction in volume of the hemithorax that high positive pressures are built up and cause actual compression of the underlying lung.

Let us return this time to our schematic diagram for a further consideration of this dynamic factor in the production of delayed selective collapse. In figure 11 we have a hemithorax in which the upper lobe is the seat of a bronchopneumonic infiltration. At *A* we see the inspiratory position after the introduction of four volumes of air. We see that the upper lobe has lost but one volume while the lower lobe has lost three volumes. At *B* we see the situation on expiration. Here the upper lobe, being more difficult to compress, has lost but two volumes, the rest of the loss being assumed by the lower lobe. At *C* the upper lobe is more difficult to reëxpand than it was to compress, and it regains only one of the two volumes lost during the previous expiration. Again the lower lobe compensates for the remainder of the total volume changes. It should be noted here that even at this early stage the lower lobe is hyperfunctioning, and its excursion, between inspiration and expiration, is greater than under normal conditions. This procedure of compression, with only partial reëxpansion, continues with each respiratory cycle. Between *E* and *F*, a refill has been given, which raises the total pneumothorax to eight volumes. At *K* and *L* we see expiration and inspiration of a maximum amount of selective collapse, and we note that the lower

lobe at *L* is just off the lateral chest-wall. At *M* we have the inspiratory position after the absorption of two volumes of air from the pneumothorax space. We see that the lower lobe is against the chest-wall and that the further volume change has necessitated a partial reëxpansion of the upper lobe. The clinical application of this is that, in maintaining a maximum selective collapse, sufficient air should be kept in the pleural cavity to keep the functioning healthy lobe off the lateral chest-wall

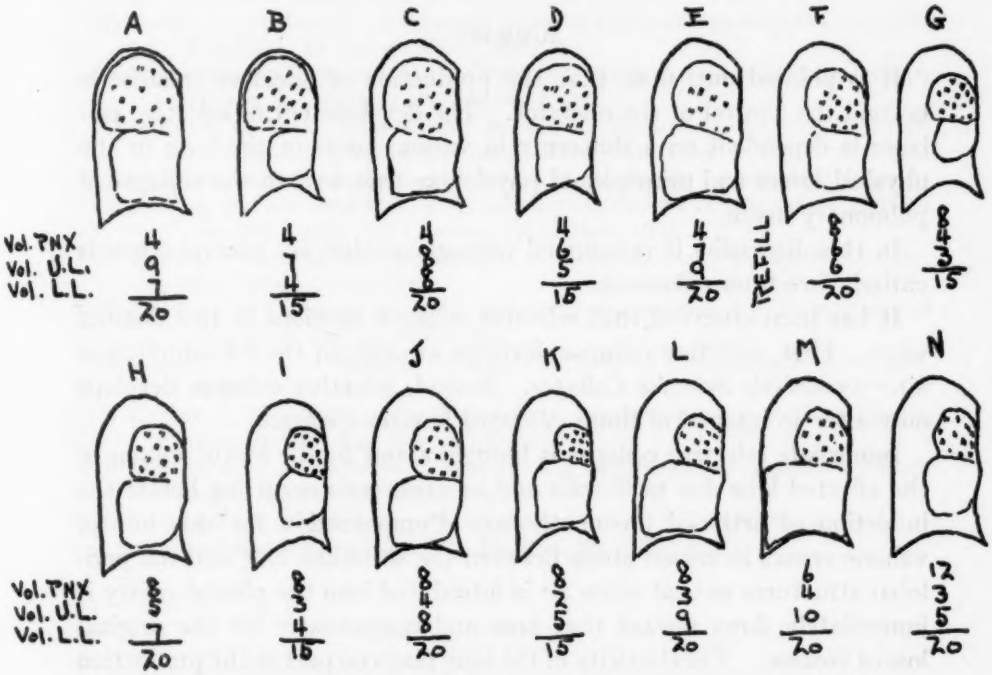

FIG. 11. Diagrammatic schema of a hemithorax showing the development of delayed selective collapse when one lobe is the seat of a bronchopneumonic infiltrative lesion.

during full inspiration. At *N* we note a further refill that has changed the selective collapse into a beginning complete collapse.

The type of case used as illustrative of this mechanism of development of selective collapse is a bronchopneumonia, which condition probably leads to the most efficient operation of the factors involved. There must, however, be a degree of infiltration that will give a maximum amount of selective collapse; this will be somewhere between no infiltration, and therefore no selective feature, and complete consolidation and the inability of the lobe to collapse at all. At times the full development

of selective collapse must await the resorption of part of the exudate, and during this time a certain amount of fibrosis and/or atelectasis may develop. In such a situation the two mechanisms leading to selective collapse augment each other. I have presented the extremes of these two mechanisms; these extremes may be combined in any proportion in the general run of cases, and in all probability the pure case of one or the other is rare. After all, it is only the mechanism that differs, the end-result is the same.

SUMMARY

It is pointed out, first, that the production of selective collapse is beyond the control of the operator. The development of selective collapse is dependent on a difference in various parts of the lung in the physical forces and principles of physiology that lead to the collapse of pulmonary tissue.

In this discussion it is assumed throughout that the pleural space is entirely free from adhesions.

It has been observed that selective collapse develops in two distinct ways. First, selective collapse develops at once on the introduction of air,—*Immediate Selectice Collapse.* Second, selective collapse develops only after an interval of time,—*Delayed Selective Collapse.*

Immediate selective collapse is brought about by the loss of volume of the affected lobe due to fibrosis and/or atelectasis occurring before the induction of artificial pneumothorax. Compensation for this loss of volume causes increased stress between the shrunken lobe and the perilobar structures so that when air is introduced into the pleural cavity it immediately flows toward that area and compensates for the original loss of volume. The elasticity of the lung plays no part in the production of this type of selective collapse. This is by far the most common type of selective collapse because in most cases some degree of fibrosis and/or atelectasis has occurred before artificial pneumothorax is attempted.

Delayed selective collapse is the type described by most authors and they have invoked the elasticity of the lung in various ways to explain its development. Generally they have predicated an increased elasticity, but we cannot increase the elasticity of the lung, especially by a disease process. Simple loss of elasticity leads to emphysema. If, however, there is an infiltrative process along the lines of elastic recoil this will increase the inertia of the lung, making it difficult to collapse and even more difficult to reëxpand.

Such an infiltrative process is best seen in early bronchopneumonic dissemination of a tuberculous lesion into one lobe. When we induce artificial pneumothorax in such a patient, we find that at first the healthy lobe is more compressed than the diseased one, and it is only after an interval of time that a selective collapse of the diseased tissue comes about.

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A REVIEW OF ONE HUNDRED REËXPANDED CASES OF ARTIFICIAL PNEUMOTHORAX[1]

EDWARD PERCY EGLEE AND OSWALD R. JONES

It is our aim in this report to discuss one hundred cases of pneumothorax that have been brought to a successful conclusion, and, in the light of our experience and study, to attempt an answer to several questions pertaining to pneumothorax therapy and its termination. These 100 cases have been derived in about equal proportion from our office practice and from Bellevue Hospital Pneumothorax Clinic. The unsuccessful cases, those in which no free pleural space was found, and those cases abandoned for various causes after a short duration of collapse, are not included.

It is almost impossible to state what percentage of the total number of pneumothorax patients these hundred represent, for many were lost, some died, while a great number were transferred to other clinics, or to surgery.

Eighty-five per cent of our cases were under forty years of age, while only 2 per cent were above fifty years.

The known duration of their disease prior to collapse, varied from a few days to over two years; and it is interesting to note that nearly all of the patients, whose disease was over two years' duration prior to collapse, had their pneumothorax instituted from ten to fourteen years ago when this method of treatment was less widely used.

The original lesions of the entire group can be divided according to their predominant pathological types into:

Fibrocavernous lesions	50	Exudative	6
Caseocavernous lesions	22	Acute pneumonic	4
Productive	10	Unknown	8

The duration of cure before collapse includes those patients whose period of bed-rest was less than one month, up to a period of two years. Sixty-six per cent were on bed-rest in sanatoria or hospital less than six months.

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Failure to improve, plus the presence of a cavity, constituted the reason for collapse in the majority of cases. Only three were collapsed because of pleurisy with effusion, and four whose lesions were of the acute pneumonic type.

Either during the course of their treatment or during the period of lung expansion, 74 per cent developed clear fluid. An additional 8 per cent developed cloudy fluid, which on direct smear showed tubercle bacilli. Two per cent became secondarily infected and had to be treated with gentian-violet. We were unable to demonstrate the presence of fluid at any time in 16 cases. Adhesions were present in 60 cases, broad in 36 and string-like in twenty-four. Positive pressures proved effective in 28 cases. Pneumolysis was used in two cases.

TABLE 1

Fluid during collapse

TYPE	NUMBER OF CASES
Clear	74
Tuberculous empyema	8
2d infection	2
No fluid	16
Total	100

Frequent sputum examinations were made, and the time necessary to obtain a negative sputum report noted. Thirty-nine per cent became negative within three months, and seventy-four per cent before the end of a year. All presumably negative sputa were examined by the concentration method.

Seventy-eight per cent of the cases completely reëxpanded within one year after pneumothorax had been discontinued. Eight cases have not wholly reëxpanded even though treatment was discontinued two years ago. The number of years after expansion in this group averaged 3.2 years. Forty-three cases have been expanded under three years and fifty-seven for more than three years. The majority of cases after re-expansion showed considerable fibrosis and calcification of their original pulmonary lesions. Thirty-two patients were left with a fibrothorax, and ten with pleural fibrosis together with some fluid. Bilateral pneumothorax was used in 6 cases with very excellent results.

The duration of collapse treatment varied from under a year up to fourteen years, with an average of 4.59 years. The great majority, or

72 per cent, were terminated because the disease was considered arrested, but 17 per cent were unintentionally terminated because of loss of space.

TABLE 2

Length of collapse

	NUMBER OF CASES		NUMBER OF CASES
Up to 1 year	2	6 to 7 years	9
1 to 2 years	8	7 to 8 years	2
2 to 3 years	17	8 to 9 years	3
3 to 4 years	27	9 to 10 years	2
4 to 5 years	23	14 years	1
5 to 6 years	6	Total	100

Average 4.59 years.

TABLE 3

Condition of lung on reëxpansion

TYPE OF ORIGINAL LESION	FIBRO-CAVERNOUS	CASEO-CAVERNOUS	EXUDATIVE	ACUTE PNEUMONIC	PRODUCTIVE	UNKNOWN	TOTAL
Diffuse pleural fibrosis	22	5	3	3	3	4	40
Partial fibrosis of pleura	15	2	1		5		23
Marked mediastinal distortion	*Most of them*						
Diffuse fibrosis of pleura with encapsulated fluid	6	4	0				10
Slight fibrosis of pleura with encapsulated fluid	4	3	2		1		10
No change in pleura except over area of scars	7	8		1	1		17
Total	54	22	6	4	10	4	100

TABLE 4

Number of years after expansion

	NUMBER OF CASES		NUMBER OF CASES
Less than 1 year	8	Unsuccessful	4
1 to 2 years	28	Not known	1
2 to 3 years	17	Died	1
3 to 4 years	12	Spread to other lung	1
4 to 5 years	13	Total	100
More than 5 years	15		

Average 3.2 years.

Three cases developed positive sputum after termination, and these were controlled by thoracoplasty in one, and phrenicectomy and thoracoplasty

in the others. One developed a positive sputum two years after reëxpansion; phrenicectomy in this case converted the sputum and closed the reopened cavity. The sputum has now been negative for three years. One patient died two years after reëxpansion because of generalized tuberculosis.

In the light of our study, we raise the following questions and attempt the answers:

1: Should the institution of pneumothorax be an ambulatory procedure? Looking upon this not from the public health viewpoint, but as a matter of individual welfare, we do not believe that pneumothorax should be done in this manner. In all cases a period of clinical observation is necessary. Many cases resolve upon bed-rest alone, and there is absolutely no way of determining in advance which cases will heal upon bed-rest and which will need collapse therapy.

Collapse of the exudative-type lesion or the acute case should always be carried on in conjunction with bed-rest. We believe that all cases of positive sputum should be kept in bed until the sputum has been rendered negative or until some other method of collapse therapy has been decided upon. It would seem that a period of four to six months was sufficient for a pneumothorax trial, after which, if the sputum continues positive, other forms of collapse therapy ought better be considered.

If for any reason collapse must be made ambulatory in any case of pulmonary phthisis, it might be permitted in the chronic type when the patient presents himself with a manifest cavitary process associated with few clinical symptoms. But even in such a case, pneumothorax is better instituted as a hospital procedure.

2: When should pneumothorax be instituted? This is of course the most crucial question. As put here, this question refers to the time rather than to the type of lesion. However, we could not properly answer this question without briefly outlining first our concept about the indications of pneumothorax in general.

We recognize, first, immunobiological and, second, mechanical indications for pneumothorax.

The immunobiological indication is present in every active phthisis lesion which gives rise to clinical phenomena of infectious illness. While this is most clear-cut in fresh pneumonic lesions when prostrating toxaemia is the sign of acute infectious disease, phenomena of more or less acute infectious illness may be present also in the case of more chronic productive lesions when the process has reached such an extent that in its

exacerbation it appears in the form of bronchopneumonic phthisis. Here pneumothorax actually blocks the toxaemia and shifts the immunobiological balance in favor of the patient, and localizes the lesion.

The mechanical indication for pneumothorax is present in every case of chronic productive phthisis in which immunobiological stabilization has occurred spontaneously, yet the constantly positive sputum and particularly the presence of a tissue defect (cavity) are of such nature and extent as to make spontaneous final healing of the lesion unlikely. Here pneumothorax aims to prevent bronchogenic dissemination of bacilli which converts the lesion into a self-propagating process. By approximating the edges of tissue defects, pneumothorax acts chiefly mechanically in making possible healing which could hardly ever occur spontaneously. The immunobiological indications for pneumothorax are therefore to localize the lesion when it is acutely exudative. The mechanical indications for pneumothorax are therefore to localize the process when the lesion is a chronic productive one.

The immunobiological indications call for the establishment of pneumothorax at the earliest possible moment, once the nature of the process has become clear and the clinical signs and symptoms clearly indicate that extensive caseation and breaking-down is imminent. Our aim should naturally be to prevent further advance and anticipate the breaking-down of the lesion.

Pneumothorax should only be resorted to when it has become perfectly clear that the process cannot be brought to arrest without collapse therapy. It is obvious then that, with the exception of acute pneumonic processes, in most cases of phthisis a period of at least a few weeks of observation is required to establish the indications of pneumothorax. We feel on the one hand that the indiscriminate use of pneumothorax, especially its establishment on the basis of X-ray evidence alone of a chronic productive lesion in a lung, is to be strongly condemned. On the other hand, our experience has also convinced us that the diagnosis of a so-called "benign form" of exudative type of pulmonary tuberculosis is just a fiction of the mind drawn from retrospection. There is not a single reliable piece of evidence which can guide us in determining in an acute and fresh case of phthisis which way the immunobiological balance will shift. All forms of pulmonary phthisis are malignant unless they prove themselves to be otherwise.

3: Should acute pneumonic phthisis be collapsed? We raise this question particularly because of the frequent warning against collapse of this

type of lesion. We are advised to let them alone and wait with collapse at least until they have advanced to cavitation, for hasty collapse may cause the lesions to break through the visceral pleura with a resulting pyopneumothorax. We take the opposite view, as we believe that it is just here that the immunobiological indications for pneumothorax are most clear-cut. What better evidence have we of the reaction of the individual to his infection than the type of his lesion? Is it not reasonable to attempt to throw the balance in favor of the patient, since it depends upon this immunobiological balance whether the issue will be one of resolution, or one of rapid caseation of the entire lesion. There is much to gain from an immediate pneumothorax and all may be lost by delay.

We have many times been saddened by the sight of such an acute lesion spreading into the opposite side, or by a poor collapse, due to adhesions formed, because the institution of pneumothorax was delayed.

Only by the earliest establishment of pneumothorax can we hope to get ahead of the process, and prevent exhaustion of the patient's defense power by the prostrating toxaemia which must eventually overwhelm him. Only by a timely collapse can we get ahead of the process of caseation and prevent spread of the lesion to an extent where it can no longer be brought under control. The induction of pneumothorax here should be slow, giving time for the expulsion of the already caseated and liquefied tissue. Many acute pneumonic lesions are as dense as pneumococcic inflammations and are difficult to collapse. But these lesions, if surrounded by air, many times become less toxic, and resolve slowly, and then the collapse becomes more effective over the caseated areas.

4: How does pneumothorax effect healing? When speaking of the effect pneumothorax has upon healing, we must take into consideration the process of healing without the aid of collapse therapy and try to determine whether these processes are favorably or harmfully influenced by the induction of pneumothorax.

Healing of tuberculosis takes place either by resolution or by fibrosis and calcification. Genuine healing of the lesions under the effect of pneumothorax takes place really only in acute exudative processes. Chronic productive processes represent *per se*, and to begin with, already naturally healing lesions. Yet because of the bronchogenic dissemination of bacilli, these lesions tend to continue in the characteristic self-propagating process. Here pneumothorax does not really effect healing of the existing lesion, but, by preventing dissemination, and thereby the

progress of the natural healing of present lesions, the disease as a process is finally healed.

Healing of the lesions in acute exudative processes is effected under pneumothorax by turning the immunobiological balance in favor of the patient.

Healing of the process in chronic productive phthisis is effected under pneumothorax by mechanical approximation of the walls of tissue defects and mechanical blocking of the pathways through which the bacilli are disseminated.

From our experience we must conclude that the healing of lesions is not hastened by pneumothorax. While pneumothorax often makes possible healing where it could not occur spontaneously, yet when spontaneous healing does occur it is more rapid and perhaps even more complete than is healing under pneumothorax.

Experience has also taught us that even the healing of the process as a whole is not materially shortened under the effects of pneumothorax. The average length of cure under collapse is not shorter than without it; but, if we compare the percentage of cures with and without collapse, it becomes obvious that healing of the process can be obtained more often only by collapse.

5: What is the evidence of healing under collapse? Issuing from the known biological fact that healing in tuberculosis does not occur until the toxicity of the lesion has been abated, we are justified in assuming that, when the individual shows no clinical symptoms of his disease, and the X-ray evidence of his collapse is satisfactory, the collapsed lesion is healing. In cases of bilateral lesions in which pneumothorax was established in the more involved side, it has been our experience that healing in the collapsed lung could frequently be followed by the parallel progressive absorption of the lesions in the noncollapsed side. In a case of chronic productive phthisis, in which the indication for pneumothorax was an entirely mechanical one, we cannot expect any positive signs of healing, since this depends entirely on the efficiency and the length of time the collapse is maintained. Negative sputum is a favorable sign but no definite criterion of a healed lesion under collapse treatment, for we know how long bacilli can remain viable in locked-up lesions. Safe encapsulation of the bacilli is a matter of time.

6: What are the criteria of a successful collapse? A collapse can be judged as successful by its results. While the criteria of unsuccessful collapse are very obvious, there are no reliable evidences of the positive

success of a collapse while it is maintained. Strictly speaking, we may date our successful collapse from the disappearance of symptoms, a favorable X-ray, and from the conversion of the sputum, yet even these do not guarantee the ultimate success of the collapse. From our experience we have come to rely upon what we have termed the "cold test." It is a well-recognized fact that continued negative sputa may become at least temporarily positive when the patient suffers a mild respiratory infection. It has been our experience that if patients have passed through several such periodic colds without reversion of their sputum, they may be confidently considered as having become permanently sputum-negative cases.

On the whole, it might be said that a successful collapse is probably best judged by the rapidity with which a positive sputum is converted into a negative one. In our series, 60 per cent were converted within six months, and of these only two failed to show persistently negative sputum and none developed a spread to the contralateral lung.

We believe that pneumothorax therapy should not be continued for more than four to six months if after that length of time the sputum has failed to become negative. It is much better to institute some other form of collapse therapy at this juncture, such as phrenicectomy, the Jacobaeus operation or thoracoplasty, rather than continue treating a patient for a longer period with artificial pneumothorax.

After a period of clinical observation, collapse should be started in conjunction with bed-rest; and it is our belief that bed-rest should be an adjuvant of collapse therapy until such time as the sputum has been converted. This at times is not practical, and is impossible of application; but, when so carried out, the resulting contralateral spreads are less. In any event, collapse, when instituted for the immunobiological control of exudative lesions, should be accompanied by bed-rest until all clinical symptoms have disappeared. The same idea should apply to the productive type, in which collapse is of mechanical aid in the closure of cavities. After this period is reached, the patient may become ambulatory; and at this time great care is necessary, especially when dealing with clinic patients, to impress upon them the necessity for continued treatment. It has been our method to X-ray all patients every six to eight weeks and to examine sputum every four weeks, all sputa, negative on plain smears, to be examined by the method of concentration.

Blood sedimentation is a routine procedure at three-month intervals. Although several thousand examinations have been made, no attempt at

correlation of results has been attempted beyond the fact that no cases have been expanded with persistently high indices. Blood reactions after the manner of Medlar have not been used, nor has the tuberculin test as suggested by Neil.

7: How long should pneumothorax be continued? Concerning this question, we have very little information. Those cases collapsed because of immunobiological indications will no doubt require a shorter period of time than those collapsed because of the necessity for mechanical aid. The literature contains varying opinions as to the time necessary for collapse, but the average is in the neighborhood of three years, while our series averages four to five years. The tendency is still upward, but an average of three to five years is at present considered adequate. Ample cases are on record in which collapse periods of from five to seven years proved inadequate. That collapse periods of even below two years quite often prove adequate is a well recognized fact of experience. A considerable number of cases are also on record in which collapse periods of below one year sufficed. However, indiscriminately as pneumothorax has often been used, one cannot be sure how many of these were such in which the lesion would perhaps have healed spontaneously in even a shorter time and the indications for pneumothorax probably did not exist.

If we analyze the problem from the standpoint of the strict indications for pneumothorax, theoretical considerations lead us logically to the conclusion that, just as the indications for establishment, so the indications for the length of its maintenance must depend upon the type and extent of the lesions. Our assumptions here which hark back to the twofold indications of pneumothorax are as follows:

The more purely immunobiological the indications for pneumothorax were, the shorter may the duration of it be planned, and the more purely mechanical the indications for pneumothorax were, the longer must its maintenance be contemplated. In other words, in the case of a pneumothorax established at the earliest possible moment in an acute exudative lesion before breakdown has occurred, termination may be attempted in less than two years. The more certain we can be that the pneumothorax was established before breakdown has occurred, the more confident we may be that absorption has been completed. We know that most exudative lesions, if they are going to clear, do so on bed-rest alone, within three to six months. In order to heal the remaining tissue destruction, we have allowed another one to one and a half years more for safety.

Unfortunately, it is rarely so that such acute exudative lesions can be collapsed before considerable caseation has already occurred. The result is that even after the extensive infiltration has become absorbed under the pneumothorax, there persists a variable number of caseous foci of variable size which must become encapsulated by a heavy enough fibrotic ring to make the patient safe against immediate exacerbation upon reinflation. In the presence of such foci, after the bulk of the lesion has cleared, we are facing exactly the same situation as if we had established the pneumothorax for mechanical indications.

In pneumothorax established for purely mechanical indications, the duration of the pneumothorax depends largely upon the size of the defect. A small cavity may be expected to heal over and be safely closed in a successful collapse period of two to three years. With a large tissue defect or large caseous focus, a safe degree of healing cannot logically be expected in less than five years or more.

We do not consider the length of time a sputum has remained negative, while the lesion is successfully collapsed, to be an infallible guide in the question of when to terminate collapse. If the collapse is successful, it is only natural to expect the sputum to become negative soon and remain negative as long as the collapse is efficient. The negative sputum under these conditions does not tell us everything about the process of healing under the pneumothorax. What we know about the length of time tubercle bacilli will remain viable in locked-up lesions in the body should make us realize that we can only rely on the safe encapsulation of the lesions, and this in turn can only be brought about by successful collapse carried over a sufficient period of years.

8: Is obliterating pleuritis following termination harmful or helpful? It was noted that the great majority of the expanded cases, regardless of the original lesions collapsed, showed varying degrees of pleural fibrosis. The question naturally arises as to whether this obliterating pleuritis is harmful or helpful. Many of our cases were unintentionally terminated because of loss of space due to obliterating pleuritis. In many instances these cases were terminated much sooner than was desired. In some instances, this followed after less than one year of collapse therapy. When we consider that so many of these cases remained permanently well after such a short collapse period, we wonder what part the obliterating pleuritis could have played in the ultimate result. We believe, however, that pleural effusions with resulting obliterating pleuritis play a mechanical rather than an immunobiological part in the production of

successful results after reëxpansion. In all of our cases ending up with obliterating pleuritis, the expanded lung became smaller, the pleural space contracted, the mediastinum was drawn into the affected side, and, in addition, a small amount of fluid usually remained encapsulated. All of this served to immobilize the reëxpanding lung and to prevent reopening of the lesions and defects. It would seem, then, that such beneficial effect as obliterating pleuritis might have had was essentially mechanical. Contrary to those who object to pneumothorax therapy because it causes pleural effusion resulting in obliterating pleuritis, our experience leads us to believe that these complications are not altogether undesirable.

9: The treatment of tuberculous empyema: The principal object in the treatment of tuberculous empyema is to obliterate the pleural space. For this some advocate surgical collapse as the only method of treatment, but, as we have observed, even this fails to close the space and the pocket of fluid frequently remains. We suggest that if the pleural infection can be controlled by simply aspirating it, the lung should be kept collapsed until the proper date for reëxpansion. However, if the infection cannot be held in check, or a bronchopleural or chest-wall fistula develops, then thoracoplasty is the procedure which should be used. If the lung fails to reëxpand, and the pleural infection persists, we again advocate surgical collapse.

10: Coöperation between clinic and hospital: In dealing with a large number of clinic patients, one very important factor has become apparent in order to ensure proper management. Within the last few years, several pneumothorax clinics have been established in the large cities throughout the country. A few of these clinics are in close coöperation with hospitals, but unfortunately most of them are not. We all know that each individual in whom pneumothorax is established presents, during the continuation of treatment, problems which can only be handled by the timely institution of other methods of collapse therapy in lieu of failure of artificial pneumothorax. We have all seen cases of pneumothorax carried on not only for several months, but for several years, in the fruitless effort of trying by this method alone to establish a negative sputum, and only too often has the result been a spread to the contralateral lung. If clinic and hospital coöperation is such that their individual problems can be immediately referred, then many otherwise unsuccessful results are obviated. No clinic should undertake the treatment of the pneumothorax patient unless such a clinic has ready and easy

access to the surgical wards of a chest-hospital service. We feel that the utmost condemnation should be given to the establishment of pneumothorax squads whose duty it would be to travel from town to town, inducing pneumothorax without the remotest possibility of being able to carry more than the exceptional case to a successful termination.

Those most interested in pneumothorax as a public-health measure will no doubt disagree, and point to the number of sputum conversions so obtained. Certainly the better approach for public-health purposes would be an increase in the number of beds.

11: Pneumothorax and pregnancy: That pneumothorax therapy has eliminated many of the problems arising in the pregnancies of tuberculous women has been sufficiently emphasized before. However, the psychological and social implications of raising the families of these patients with the aid of pneumothorax have to our knowledge never been presented in their true light. It has particularly never been emphasized that, since it is just as unsafe for tuberculous women to weather pregnancies after as before pneumothorax therapy, if a tuberculous woman is to have a family, the most ideal time to have her pregnancies is just during the pneumothorax treatment, when her lesions are under better control than at any time before or afterward. We speak so much these days of the somatic effects of the psychic experiences of our patients, yet we do not fully appreciate the necessity of restoring these tuberculous women to psychological and social equality with their fellows by enabling them to complete their obligation to their homes.

Most of us have under our care a large number of young married women who have their lives to lead and their happiness at stake. Are we going to forbid them to have children for the entire length of their illness, which includes a collapse period of four to five years and another one or two years of waiting after the reëxpansion? Is it not more logical and purposeful to permit or perhaps even advise them to have their children during the years of the collapse period and then let their lungs reëxpand after their families are completed.

Our procedure has been as follows: If they become pregnant prior to stabilization of the disease, we do not allow its continuation. After they have become stabilized, we permit them to become pregnant and continue their collapse through one or more pregnancies, after which their lungs are allowed to reëxpand, provided their disease has become arrested. This we follow with the advice that in the postcollapse period pregnancies are less safe, since they must rely on the healed condition of the lungs.

The most important question that is usually asked by the pneumothorax patient is how soon after the institution of pneumothorax will he be permitted to return to work. This question in the individual case is always difficult to answer, and is always dependent upon the success of the collapse, which again is dependent upon the time necessary for conversion of the sputum. We feel that no patient should be allowed to return to work unless his lesion is apparently arrested. The great rise in the patient's morale when told he or she may work, offsets what little harm the increased physical activity might cause. The present economic state of most patients forces all of us to determine the earliest possible date of return to work.

THE FREQUENCY OF ARTIFICIAL-PNEUMOTHORAX REFILLS IN TUBERCULOSIS

A Preliminary Report[1]

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Since the inception of pneumothorax therapy, there have been variations in opinion as to the proper size and frequency of refills. Forlanini advocated that the pneumothorax be established and maintained by means of the frequent introduction of small amounts of gas into the pleural sac. He introduced the gas by piercing an intercostal space with a small needle. Brauer and Murphy introduced much larger amounts of gas at infrequent intervals. Brauer reached the pleura by incising the overlying tissues. Murphy introduced gas by means of a cannula. Though the methods of Brauer and Murphy had considerable popularity in this country for many years, modern pneumothorax therapy is based upon Forlanini's principle of the use of relatively small, frequent refills.

In the average practice of to-day, provision is made for the introduction of from 200 to 400 cc. of air into the pleural sac during the initial induction of the pneumothorax. This is repeated on the second and third days; then refills of 300 or 400 cc. of air are given twice each week, or perhaps only once weekly, until either the desired collapse of the pulmonary lesion is obtained, or complications necessitate the use of a longer interval, or the pneumothorax is proved to be unsatisfactory. A study of the literature has brought to light no mention of any policy of using refills more frequently than is described above as the "average practice" of to-day.

Physicians using such a method of managing therapeutic pneumothorax are familiar with the partial reëxpansion of the lung which occurs between refills, especially during the phase of active collapse of the pulmonary lesion. Theoretically, it would seem that any method of managing therapeutic pneumothorax which allows appreciable reëxpansion of the lung between refills is scientifically unsound, for reasons as

[1] From the Tuberculosis Service of Dr. John M. Nicklas, Grasslands Hospital, Valhalla, New York.

follows: *1:* The alternate compression and relaxation of the pulmonary tissue would increase the circulation of the blood and lymph through the tissue, thus promoting the liberation of toxins and the dissemination of bacilli from the lesion and preventing the ischaemia in the lesion which is presumed to be favorable to fibrosis. *2:* The almost constantly changing anatomical status of the pulmonary lesion would tend to prevent the organization of delicate young strands of connective tissue into mature fibrosis. *3:* The larger refills at longer intervals, resulting in sudden extreme changes in the position of the heart and great vessels and the pressure upon them, would tend to produce circulatory embarrassment. *4:* The sudden changes in respiratory capacity and the pressure upon the heart and great vessels might be considerable factors in the production of the discomfort which patients often experience during the active collapse of the lung by the usual method. *5:* The frequently alternated tension and relaxation of pleural adhesions would seem to be a less efficient factor in stretching them than a constant uniform tension. *6:* The alternate compression and reëxpansion of the tissue about a cavity would seem to be less favorable to its closure than a steady, uniform compression.

These purely scientific reasons would seem to require the use of refills of such size and frequency as to obtain a uniformly progressive type of collapse and to prevent reëxpansion between refills. In addition, it occurred to us that frequent refills should shorten the time required to obtain a satisfactory collapse of the pulmonary lesion, or to prove the ineffectiveness of the pneumothorax, thus relieving somewhat the financial and social burden of the treatment of tuberculosis. It is common experience that for the average pneumothorax-treated sanatorium patients, having the usual proportion of approximately 30 per cent moderately advanced lesions and 60 per cent far advanced lesions, a minimum period of two months and an average period of six months are required to obtain a satisfactory collapse of those lesions which can be collapsed by pneumothorax given by the usual methods.

It is probably the average opinion, certainly it is a desirably conservative one, that most patients with moderately advanced lesions and all patients with far advanced lesions should be on strict, or only slightly modified bed-rest on a sanatorium type of regimen until a satisfactory collapse of the pulmonary lesion has been obtained. When this requires an average period of six months of sanatorium residence, the serious economic burden of the treatment of pulmonary tuberculosis has been

decreased too little by the use of pneumothorax, because McMahon and Kerper (1) have shown that six months is the average period required for the spontaneous closure of cavity. A large majority of patients are unable to pay for a six months' period of treatment in a private sanatorium and often must wait several months for admission to the tax-supported or endowed institution, because of the relatively slow "turnover" of patients and insufficient number of beds in these institutions. During this period of waiting, lesions frequently become too far advanced for successful treatment, not to mention the prolongation of contact of sputum-positive patients with the public. Therapeutic pneumothorax is the only method of treatment yet known by which the period of bed-rest can be shortened, yet the results of the usual methods of its management are still slow enough of realization as to present a serious economic problem to the patient, the taxpayer, and the hospital executive.

Increased rapidity of collapse of pulmonary lesions by pneumothorax is desirable, not only because the patient whose tuberculosis is satisfactorily controlled is returned to society sooner, but also because the period of trial of pneumothorax in those cases in which the procedure proves ineffective is ended sooner and delay in using supplementary methods of collapse therapy is avoided.

A possible objection to such frequent refills which might be raised on scientific grounds is that the incidence of certain complications of therapeutic pneumothorax, such as pleural effusions and spontaneous rupture of the visceral pleura, might be increased. It seems to us more reasonable to assume that the more uniform progression of the pulmonary collapse, which is obtained by frequent refills, would tend to decrease the incidence of these complications rather than to increase them. A longer period of study than that covered by this report will be necessary to determine the answer to this question.

An objection to the use of frequent refills which could be raised on economic grounds is the additional cost of the extra treatments. Within the sanatorium and in the outpatient clinic this problem can be met by a reapportionment of staff activities. Since the phase of active collapse of the pulmonary lesion most often is spent in the sanatorium, the problem becomes relatively unimportant. The physician in private practice who begins pneumothorax in his office or in the patient's home could distribute the financial burden of frequent refills by quoting monthly rates for treatment.

Prior to July 26, 1935, pneumothorax refills in Grasslands Hospital

were given according to the routine already described as the "average" method. Since that date it has been routine practice to give refills of appropriate size every day, until either a satisfactory collapse of the pulmonary lesion is obtained, or the pneumothorax is proved unsatisfactory, or complications necessitate the use of a longer interval between refills. When such complications as pleural pain, respiratory discomfort, extreme displacement of the mediastinum, alarming loss of weight, or pleural effusion make it necessary to decrease the vigor with which collapse of the pulmonary lesion is pursued, the reduction of the tension of the pneumothorax is obtained by first reducing the amount of each refill to a minimum of from 50 to 100 cc. of air. Not until the full effect of reducing the amount of the refill has been realized is the interval between refills lengthened. A satisfactory collapse of a pulmonary lesion is maintained by the same general policy of short intervals between refills.

During the period of ten months since this policy of managing therapeutic pneumothorax was begun, certain observations have been made which are thought to be worth reporting. It is realized that a complete analysis of the use of frequent refills is not now possible because of the small number of cases reported and the short period of time that the pneumothoraces have been in effect. These cases are reported only as a preliminary to a later more complete report, with the desire to stimulate interest in the method and encourage other reports on its use.

The cases in which pneumothorax was attempted are classified as follows: *1: Operative Failure* (*OF*): those cases in which no free pleural space, or only a small, inoperable space could be obtained. *2: Therapeutic Failure* (*TF*): those cases in which an operable pneumothorax was obtained, but the pneumothorax alone was not sufficient to collapse the pulmonary lesions satisfactorily. *3: Therapeutic Success* (*TS*): those cases in which the pulmonary lesions were satisfactorily collapsed by pneumothorax alone. *4: Incomplete* (*I*): those cases in which the period of treatment is too short to determine whether their classification is *TF* or *TS*.

Each pneumothorax is listed as one case. Thus, a bilateral pneumothorax is represented as two cases. The criteria of *Therapeutic Success* are as follows: (1) all excavated areas in the collapsed lung are no longer demonstrable by fluoroscopic and roentgenographic examinations, and (2) tubercle bacilli are consistently absent on two or more consecutive monthly examinations of specimens of sputum collected over a period of

three days each. These examinations are made after concentration of the entire specimen, and all examinations are done by the same person. The criterion of "negative sputum" is abandoned, and fluoroscopic and roentgenographic examinations are relied upon for evidence of closure of cavity in all cases having lesions which are potential sources of "positive sputum" in the lung contralateral to the pneumothorax under consideration.

The study covers an analysis of all pneumothoraces attempted for the treatment of pulmonary tuberculosis in adults in Grasslands Hospital during the period of six months from the end of July, 1935, to the end of January, 1936. During this period attempts were made to induce 69 pneumothoraces in 65 patients. (Pneumothoraces were attempted bilaterally in four patients.) Of these 69 attempted pneumothoraces, no free pleural space was found in sixteen, which were labelled *Operative Failure* (*OF*). Thus 53 operable pneumothoraces were analyzed to determine the results of the policy of using frequent refills. All lesions for whose collapse these pneumothoraces were induced contained cavities that were demonstrated roentgenographically. Tubercle bacilli were found in the sputum of every patient before pneumothorax was induced. The pneumothoraces were managed by six physicians who used essentially the same technique and did the work as part of the hospital routine. Fluoroscopy of each patient was done routinely once each week. Additional fluoroscopic examinations were made whenever the need arose. In so far as the X-ray budget and laboratory personnel permitted, it was a routine policy that, as soon as fluoroscopy revealed that all cavities in the treated lung were collapsed, a roentgenogram was made and a concentrated three-day specimen of sputum was examined for tubercle bacilli. If study of the roentgenogram revealed no evidence of cavity in the collapsed lung, and if that sputum examination, as well as another done one month later, revealed no tubercle bacilli, the date of cavity closure was estimated as the date of the roentgenogram. Sputum reports were disregarded as criteria of cavity closure whenever a lesion in the lung contralateral to the pneumothorax was a potential source of tubercle bacilli. It is thought that the estimate of the average period of time required to close cavity is quite conservative, because in many cases several weeks elapsed after fluoroscopic examination revealed cavity closure before the roentgenograms were made.

Ten months have elapsed since the first pneumothorax in this series was induced, and four months since the last. All pneumothoraces were

TABLE 1

Analysis of pathological type

(69 pneumothoraces attempted in 65 patients—bilateral in four)

PATIENT	SEX	PNEUMOTHORAX SIDE	RIGHT LUNG		LEFT LUNG	
			Classification	Results during active pneumothorax	Classification	Results during active pneumothorax
WN	M	L	FA.P.C2	Unchanged	FA.P.C3	OF
AS	M	R	FA.E.C4+	OF	MA.E.	Unchanged
MM	M	L	Clear	Unchanged	FA.P.C3	OF
VD	M	RL	FA.P.C4	OF	FA.P.C3	I
WJ	M	R	FA.EP.C4+	OF	FA.P.	Unchanged
GT	M	RL	MA.EP.C3	OF	FA.EP.C4+	TF
HN	M	R	FA.P.C4	OF	FA.P.C2	Unchanged
RB	M	L	MA.P.C2	Unchanged	FA.EP.C4	OF
EB	M	L	FA.P.C3	Unchanged	FA.P.C3	OF
EM	M	L	FA.P.C3	Unchanged	FA.P.C4+	OF
HE	M	R	FA.P.C4+	OF	FA.P.C3	Unchanged
LD	M	L	Clear	Unchanged	MA.EP.C3	OF
EM	F	R	MA.P.C2	OF	Min.P.	Unchanged
RT	F	R	MA.E.C2	OF	Clear	Unchanged
DB	F	L	MA.P.	Regression	FA.P.C4+	OF
TT	F	RL	FA.E.C4	OF	FA.E.C3	TF
LS	M	R	FA.E.C4+	TF	MA.E.C2	Unchanged
JG	M	L	MA.E.	Unchanged	FA.P.C4	TF
HH	M	L	MA.P.C2	Unchanged	FA.P.C4	TF
WW	M	R	FA.EP.C4+	TF	MA.P.C2	Unchanged
AM	M	L	FA.E.C3	Unchanged	FA.E.C4+	TF
BP	F	L	Clear	Unchanged	FA.P.C4+	TF
EB	F	R	FA.E.C4	TF	Clear	Unchanged
DK	F	L	MA.E.C2	Regression	FA.E.C4+	TF
MC	F	L	MA.E.	Progression	FA.E.C4+	TF
RB	F	R	FA.E.C2	TF	MA.E.	Progression
WH	M	L	MA.P.C2	Regression	MA.E.C3	TS
JB	M	R	FA.E.C4	TS	MA.P.	Regression
GM	M	R	MA.P.C2	TS	Clear	Unchanged
JL	M	R	FA.P.C4	TS	MA.P.C3	Unchanged
EP	M	R	MA.E.C3	TS	Clear	Unchanged
TQ	M	L	FA.P.	Unchanged	FA.EP.C4+	TS
JD	M	R	FA.E.C2	TS	Clear	Unchanged
HV	M	R	MA.EP.C3	TS	Clear	Unchanged
TF	M	L	MA.P.C2-TSpnx	Unchanged	MA.P.C2	TS
JB	M	L	FA.P.C2	Unchanged	FA.EP.C4+	TS
CT	F	RL	FA.EP.C4	TS	MA.E.C3	I
CS	F	R	MA.E.C2	TS	MA.EP.C2-TSpnx	Unchanged
GW	F	L	Clear	Unchanged	MA.E.C3	TS
AC	F	R	MA.P.C3	TS	Clear	Unchanged
MC	F	R	FA.EP.C4+	TS	Min.E.	Regression

TABLE 1—*Concluded*

PATIENT	SEX	PNEUMOTHORAX SIDE	RIGHT LUNG		LEFT LUNG	
			Classification	Results during active pneumothorax	Classification	Results during active pneumothorax
FW	F	R	MA.EP.C3	TS	Min.P.	Unchanged
GL	F	R	FA.E.C4	TS	Clear	Unchanged
EK	F	R	MA.EP.C3	TS	FA.EP.C4+TSpnx	Unchanged
MF	F	R	FA.EP.C4+	TS	MA.E.C2	Regression
AD	F	R	MA.EP.C3	TS	MA.EP.C2.TFpnx	Unchanged
MC	F	R	FA.E.C2	TS	MA.E.C1	Progressive
AB	F	R	FA.E.C4+	TS	MA.E.	Regression
MG	F	L	Clear	Unchanged	MA.P.C2	TS
AB	F	L	Clear	Unchanged	MA.EP.C2	TS
FD	F	R	MA.EP.C3	TS	Clear	Unchanged
MD	F	L	Clear	Unchanged	MA.E.C2	TS
CS	F	R	FA.EP.C4	TS	Clear	Unchanged
LF	F	R	MA.P.C2	TS	Clear	Unchanged
TC	F	L	FA.EP.C4+TSpnx	Unchanged	MA.E.C3	TS
XB	F	L	Clear	Unchanged	MA.E.C3	TS
OM	F	R	FA.E.C4	TS	MA.E.	Regression
MH	F	R	FA.E.C4	TS	MA.E.	Regression
DH	F	L	Clear	Unchanged	MA.E.C3	TS
EC	M	R	FA.E.C3	I	Clear	Unchanged
AS	F	R	FA.E.C4+	I	Clear	Unchanged
TF	F	L	Clear	Unchanged	MA.E.C4	I
RS	F	L	MA.E.C1	Regression	FA.EP.C3	I

FA = Far Advanced. MA = Moderately Advanced. Min = Minimal. E = Exudative. EP = Exudative-Productive. P = Productive. Cx = Cavity diameter in cm. OF = Operative Failure. TF = Therapeutic Failure. TS = Therapeutic Success. I = Incomplete.

classified as to results during the first six months of the study, except those begun during the sixth month. For these cases one additional month was allowed.

Tables 1 to 4 are presented for the purpose of analyzing the lesions and the results in the sixty-nine pneumothoraces attempted.

Table 1 is an analysis of the pathological type present and its behavior in both lungs of each patient during the period of active pneumothorax therapy. Before we consider tables 2 and 3, in which are summarized the data in table 1, it should be noted in table 1 that the lesions in the lungs contralateral to the 53 operable pneumothoraces progressed during active pneumothorax therapy in only 4, or 7.5 per cent, of the 53 cases.

Table 2 is a summary of the clinical classification of the extent and predominant type of pathological process in each lung for the collapse

of which pneumothorax was attempted. The extent of the lesions was Moderately Advanced in twenty-seven, or 39 per cent, and Far Advanced in 42, or 60.9 per cent, of the 69 lungs under attempted pneumothorax. (No pneumothorax was attempted in cases with minimal lesions.) The lesions were Moderately Advanced in 23, or 43.3 per cent, and Far Advanced in 30, or 56.6 per cent of the 53 cases of operable pneumothorax obtained. Far Advanced lesions were present under all of the twelve pneumothoraces which were classified as *Therapeutic Failure.*

TABLE 2

Clinical classification of pathological type and results of pneumothorax

Extent of pathological involvement	Moderately advanced 27 (39 per cent of 69)				Far advanced 42 (60.9 per cent of 69)				GRAND TOTAL
Type of pathological process	E	EP	P	Total	E	EP	P	Total	
Pneumothorax attempted	12 44.4% of 27	9 33.3% of 27	6 22.2% of 27	27 39% of 69	18 42.8% of 42	11 26.1% of 42	13 30.9% of 42	42 60.9% of 69	69
Operative failure (OF)	1	2	1	4 25% of 16	2	2	8	12 75% of 16	16 33.1% of 69
Operable pneumothorax	11	7	5	23 43.3% of 53	16	9	5	30 56.6% of 53	53 76.8% of 69
Therapeutic failure (TF)	0	0	0	0	7	2	3	12 100% of 12	12 22.6% of 53
Therapeutic success (TS)	9	7	5	21 60% of 35	7	6	1	14 40% of 35	35 66% of 53
Incomplete (I)	2	0	0	2 33.3% of 6	2	1	1	4 66.6% of 6	6 11.3% of 53

E = Exudative. EP = Exudative-Productive. P = Productive.

All Moderately Advanced lesions were satisfactorily collapsed by pneumothorax.

The lesions in the 35 lungs satisfactorily collapsed by pneumothorax were Moderately Advanced in 21, or 60 per cent, and Far Advanced in 14, or 40 per cent. The predominant type of pathological process in the 12 *Therapeutic Failures* was exudative in 7, or 58.3 per cent, exudative-productive in 2, or 16.6 per cent, and productive in 3, or 25 per cent; while in the thirty-five *Therapeutic Successes* it was exudative in 16, or

45.7 per cent, exudative-productive in 13, or 37.1 per cent, and productive in 6, or 17.1 per cent.

Table 3 is an analysis of the cavities present in 69 lungs under attempted pneumothorax and the result of the treatment. Because it was thought that the distribution of the lesions in the two lungs of a patient and the presence of contralateral pneumothorax are factors whose effects must be considered in the evaluation of pneumothorax therapy in

TABLE 3

Distribution of lesions, size of cavity and results of pneumothorax

Distribution of lesions	Unilateral lesion; unilateral pneumothorax				Bilateral lesion; unilateral pneumothorax				Bilateral lesion; bilateral pneumothorax				GRAND TOTAL
Total diameter of cavity in cms.	C2±	C3-4	C4+	Total	C2±	C3-4	C4+	Total	C2±	C3-4	C4+	Total	
Attempted pneumothorax	8	12	4	24	3	17	18	38	2	4	1	7	69
Operative failure (OF)	1	2	0	3	1	5	7	13	0	0	0	0	16
Operable pneumothorax	7	10	4	21 87.5% of 24	2	12	11	25 65.7% of 38	2	4	1	7	53
Therapeutic failure (TF)	0	1	1	2 9.4% of 21	1	3	6	10 40% of 25	0	0	0	0	12
Therapeutic success (TS)	7	7	2	16 76.1% of 21	1	7	5	13 52% of 25	2	3	1	6 85.7% of 7	35
Incomplete (I)	0	2	1	3	0	2	0	2	0	1	0	1	6
Average time in weeks to close cavity	7.6	4.5	15.7	*9.2**	18	7.7	10.2	*11.9*	4.5	8.1	17.5	*10*	*10.4*
Average time in weeks to prove (TF)	—	3	4	*3.5*	4	6.3	7.1	*5.8*	—	—	—	—	*4.8*

* Italicized figures indicate averages.

that patient, the pneumothoraces analyzed were grouped as follows: (1) unilateral lesion, unilateral pneumothorax; (2) bilateral lesion, unilateral pneumothorax; and (3) bilateral lesion, bilateral pneumothorax. Of the 7 pneumothoraces analyzed in the bilateral-pneumothorax group, five were present in five patients who already had a contralateral pneumothorax induced prior to the beginning of this study and two were induced in the same patient during the period covered by this study. In a larger series of cases it would be interesting to make comparisons of the results

obtained in each of these three groups. Such a comparison in this small series of cases might be misleading. Suffice it to note that the failures of pneumothorax (both operative and therapeutic) occurred in the most extensively distributed and excavated lesions. It is of great interest that an average period of only ten and four-tenths weeks was required to obtain satisfactory pneumothoraces in 35, or 66 per cent, of the 53 cases in which operable pneumothoraces were obtained, and that an average period of only four and eight-tenths weeks was necessary to establish the fact that pneumothorax was a *Therapeutic Failure* in 12, or 22.6 per cent, of the 53 cases. In the remaining 6 pneumothoraces, treatment was

TABLE 4

Complications due to pneumothorax in the 53 operable cases

PNEUMOTHORAX COMPLICATIONS	MODERATELY ADVANCED	FAR ADVANCED	TOTAL
Pleural effusions—small, no fever	4	3	7 13.1% of 53
Pleural effusions—large, with fever	0	9	9 16.9% of 53
Traumatic pneumothorax	0	1	1 1.9% of 53
Mediastinal displacement	3	15	18 34% of 53
Ballooning of mediastinal pleura	3	6	9 17% of 53
Loss of weight	3	7	10 18.8% of 53
Gastric distrubances	3	6	9 17% of 53
Dyspnoea	0	8	8 15% of 53

begun too recently to classify the immediate results of pneumothorax for this study. It might be mentioned that in only 10, or 28.5 per cent, of the 35 *Therapeutic Successes* was the time required to collapse cavity more than ten weeks; also, that the minimum time required to secure a satisfactory collapse was 4 days (1 case), while the maximum time was nineteen and one-half weeks (1 case). The minimum time required to prove *Therapeutic Failure* was three weeks, while the maximum time was twelve weeks.

In table 4 the complications occurring in the 53 operable pneumothoraces are listed.

The following graphic case reports are presented in order to illustrate the efficiency of frequent refills in collapsing the lung.

GRASSLANDS HOSPITAL

PNEUMOTHORAX RECORD

Name: H. H. Ward: D Service: Adult T. B.

Record fluoroscopy whenever there is a change; at least once monthly. Left

FLUOROSCOPY EXAMINATION	SPUTUM	PNEUMOTHORAX (Including decompression)			
	Amount Date Result	Date	Reading before	Amt. gas	Reading after
Date: November 12, 1935 Admitted Nov. 8th with cavities totaling 4 cm. on Left and 2 cm. on Right. Fever of 101°F. first three weeks of hospitalization. Initial pneumothorax 11/15/35. M. D.	11/12 1 oz. Gaffky IV	1935 11/15	−8 −4	400	−6 −2
		11/16	−6 −3	400	−5 −1
		11/17	−6 −1	400	−4 0
		11/18	−5 −1	400	−4 0
		11/19	−5 −1	400	−4 +1
Date: November 16, 1935 Appearance on fluoroscopy before first refill given the day after pneumothorax was induced. M. D.	1½ oz. Pos.	11/21	−5 0	400	−3 +2
		11/22	−4 −1	400	−2 +2
		11/23	−4 +2	400	−1 +3
		11/24	−5 +1	400	+2 +6
		11/26	−3 0	300	+1 +4
		11/29	−3 +2	300	+3 +7
Date: November 29, 1935 Moderate dyspnea. Interval increased. M. D.	12/11 2½ oz. Gaffky II	12/3	−3 +2	400	+4 +8
		12/6	−3 +1	400	+1 +4
		12/10	−2 +3	400	+5 +8
		12/20	−3 +2	400	+3 +5
		1936 1/3	−6 0	400	0 +3
Date: December 4, 1935 Loss of 3 lbs. in weight since admission. Temperature almost normal. Diaphragm depressed. Symptoms and cavity unchanged. M. D.	1/9 2½ oz. Gaffky VIII	1/16	−7 −1	300	−1 +2
		1/17	−6 0	400	0 +4
		1/24	−4 +1	400	−1 +2
		1/31	−5 −1	400	−2 +2
		2/4	−4 −1	400	+3 +6
		2/7	0 +2	400	+2 +6
Date: February 18, 1936 Marked displacement of the mediastinum by tension pneumothorax. Diaphragm very much depressed. Surface adhesions over uncollapsed cavity. M. D.	2/13 2 oz. Gaffky VIII	2/11	−1 +4	400	+5 +8
		2/14	+1 +6	400	+8+11
		2/18	+3 +6	400	+10+12
		2/21	+3 +6	400	+9+12
		2/25	+5+10	300	+10+16
		2/28	+5+13	200	+13+20

Remarks: The time required to prove Therapeutic Failure in this case was longer than for any other case in the series. Note the daily refills of 400 cc. during the first ten days of pneumothorax.

GRASSLANDS HOSPITAL

PNEUMOTHORAX RECORD

Name: J. B. Ward: D Service: Adult T.B.

Record fluoroscopy whenever there is a change; at least once monthly. Right

FLUOROSCOPY EXAMINATION	SPUTUM Amount Date Result	PNEUMOTHORAX (Including decompression) Date	Reading before	Amt. gas	Reading after
Date: August 11, 1935 Admitted August 9th. No previous treatment. Lesion: Far Advanced Caseous Pneumonic with cavities totaling 4 cm. Patient afebrile on admission but had fever at the onset five months before. M. D.	8/13 ½ oz. Gaffky V	1935 8/22	−11 −7	425	−6 −3
		8/23	−8 −5	400	−5 −2
		8/24	−5 −3	400	−5 −2
		8/26	−8 −4	400	−5 −2
		8/27	−7 −4	400	−4 −1
Date: August 30, 1935 All cavities closed except questionable area near upper pole of hilum. Left lung improving. M. D.	9/12 Scant Neg.	8/28	−7 −3	400	−4 −1
		8/29	−4 −1	300	−3 +1
		8/30	−4 −1	400	−3 +1
		8/31	−5 −1	300	−1 +2
		9/5	−5 −1	300	−2 0
		9/7	−3 0	300	0 +3
Date: September 12, 1935 All cavities closed. Sputum negative. Patient comfortable. M. D.	10/10 Scant Neg. 11/14 Scant Neg.	9/9	−3 −1	300	−1 +3
		9/12	−4 0	300	−1 +2
		9/14	−4 0	300	−1 +3
		9/16	−2 +1	300	+2 +6
		9/21	−2 +1	300	+1 +4
		9/23	−4 +3	300	+3 +6
Date: October 9, 1935 Healthy lung in base allowed to reëxpand partially. M. D.	12/2 Scant Neg. 1/6 Scant Neg.	9/26	−3 +3	300	+2 +8
		9/30	−4 +1	300	+1 +6
		10/1	−3 +3	300	+5 +7
		10/7	−2 +3	200	0 +5
		10/10	−1 +2	200	−1 +5
		10/14	−4 +2	200	−3 +3
Date: December 23, 1935 Patient ambulatory since 11/15. Satisfactory pneumothorax. No fever at any time. Steady gain in weight since admission. (21 lbs.) M. D.	2/3 Scant Neg.	10/17	−2 +6	200	+1 +9
		10/24	−6 +1	200	−3 +5
		10/31	−4 0	300	−2 +5
		11/8	−4 +1	300	−2 +3
		11/15	−5 0	300	−3 +2
		11/22	−4 −1	300	−3 +1

Remarks: This case is presented to illustrate the rapidity with which an advanced lesion may be satisfactorily collapsed by the use of frequent refills.

GRASSLANDS HOSPITAL

PNEUMOTHORAX RECORD

Name: C. D. Ward: B Service: Adult T.B.

Record fluoroscopy whenever there is a change; at least once monthly. Left

FLUOROSCOPY EXAMINATION	SPUTUM	PNEUMOTHORAX (Including decompression)			
	Amount Date Result	Date	Reading before	Amt. gas	Reading after
Date: October 15, 1935 Pneumothorax since June of 1932. Sputum negative 1933 and 1934; positive latter part 1935 and lung reëxpanded partially, with reopening of cavities. Readmitted for more frequent refills to stretch adhesions. Lt. clear. M. D.		1935			
	10/21	10/15	−5 −1	200	+22+
	Scant..	10/18	−4 +1	150	+24+
	Gaffky	10/22	0 +7	175	+24+
	II	10/25	+4 +9	150	+24+
	Conc.	10/29	+6+10	100	+24+
Date: November 5, 1935 Adhesions stretched considerably and cavities much reduced in size. Slight displacement of the mediastinum without discomfort. This much collapse could not be obtained by weekly refills in the Out-Patient Department. M. D.		11/1	+3+10	100	+24+
	11/7	11/4	+9+16	75	+24+
	Scant	11/5	+10+14	100	+24+
	Neg.	11/7	+7+13	75	+24+
	Conc.	11/8	+14+18	100	+24+
		11/9	+12+16	100	+24+
Date: December 13, 1935 Further stretching of adhesions. All cavities closed and sputum negative since Nov. 7, 1935. Patient comfortable. M. D.		11/12	+12+16	100	+24+
	12/5	11/14	+8+16	100	+24+
	Scant	11/15	+12+16	125	+24+
	Neg.	11/17	+16+18	50	+24+
	Conc.	11/18	+14+16	125	+24+
		11/20	+10+16	100	+24+
Date: February 18, 1936 Patient gained 4 lbs. since admission and remained ambulatory. Sputum became positive again without X-ray evidence of cavity. M. D.		11/21	+12+14	75	+24+
	2/6	11/23	+4+12	125	+24+
	Scant	11/25	+10+12	100	+24+
	Gaffky	11/26	+10+14	50	+24+
	II	11/29	+14+18	100	+24+
	Conc.	11/30	+12+16	100	+24+
Date: February 20, 1935 Intrapleural pneumonolysis was approved because efficient closure of cavity by stretching the adhesions seems unlikely. M. D.		12/2	+12+16	100	+24+
	3/5	12/5	+7+12	100	+24+
	Scant	12/6	+5+10	100	+24+
	Gaffky	12/8	+12+16	100	+24+
	I	12/9	+12+16	50	+24+
	Conc.	12/11	+8+12	75	+24+

Remarks: This case is presented to illustrate the efficacy of frequent refills in a rigid pneumothorax for the purpose of increasing pulmonary collapse by stretching pleural adhesions. It also is shown that such a tension pneumothorax as this can be carried without discomfort by using frequent small refills.

DISCUSSION

The prevailing opinion, though by no means proved, is that pneumothorax promotes healing in a properly collapsed tuberculous process in the lung by putting the organ at rest and creating a state of parenchymal ischaemia which promotes fibrosis. P. N. Coryllos (2) states that these effects are only partly obtained by pneumothorax, since intrapleural pressure is not constant or evenly progressive, but fluctuates between refills. He advocates thoracoplasty as a more effective means of collapse. We have shown that sufficiently frequent refills can create a type of collapse which is evenly progressive or constantly maintained, as desired, allowing minimum reëxpansion between refills. Our brief clinical experience with frequent refills throws no light on the hypothesis that an evenly progressive or constantly maintained type of collapse is more conducive to healing than the type of collapse with reëxpansion between refills. We have shown, however, that frequent refills shorten the period of disability of the patient by shortening the phase of active collapse of the pulmonary lesion which must be gone through before healing of cavity walls can begin.

The average period of ten and four-tenths weeks, which was required to secure satisfactory collapse of pulmonary lesions in the proportion of 60 per cent Moderately Advanced and 40 per cent Far Advanced in 35, or 66 per cent, of 53 cases of operable pneumothorax, compares favorably with the average time of twenty-two weeks reported by Herben and Franklin (3) in a similar type of lesions treated by the "average" method of administering pneumothorax, and with the average experience of many operators.

Furthermore, our experience in this series of cases indicates that the use of frequent refills will shorten the period of trial of an ineffective pneumothorax, and thus lessen the delay in using supplementary methods of collapse therapy. Since the incidence of complications was low in our series of cases, it seems reasonable to assume that such early recognition of ineffective pneumothoraces and the use of supplementary collapse measures would keep the incidence of complications low. There is a tendency to-day among some physicians treating pulmonary tuberculosis to recommend thoracoplasty in certain cases of apical lesions, without a trial of pneumothorax. The argument used to support this point of view is that the ineffective pneumothorax does much harm by collapsing the healthier tissue and producing effusions which keep this

tissue collapsed and delay the use of surgery. This argument is much weakened if the ineffectiveness of pneumothorax in such cases is proved early by the use of frequent refills and the lung is then reëxpanded, or indicated supplementary collapse therapy is used without delay.

It is our common clinical experience, as shown by table 4, that the effects of frequent refills are in no way deleterious to the patient; on the contrary, frequent refills seem to be better tolerated than refills at relatively long intervals. Though approximately 6,000 punctures of the parietal pleura were made during the six months in which 69 pneumothoraces were attempted and 53 were actively continued, many patients receiving daily punctures during the first month of treatment, in no instance did needle-track infection, cerebral air embolism, or pleural shock occur. There was one case of traumatic rupture of the visceral pleura in a patient with tuberculous pneumonia, but the accident occurred during the initial induction and was probably due to puncture of the lung with the needle. The patient did not require any special treatment and the accident cannot be attributed to the "frequent refill" therapy.

Pleural effusions occurred in 16, or 30 per cent, of the 53 operable pneumothoraces. Only 9 of these, or 17 per cent, were large enough to cover the dome of the diaphragm and were accompanied by fever. The latter group of effusions all occurred in patients with Far Advanced lesions. These figures may be compared with the composite figure of 56.2 per cent incidence of effusions in therapeutic pneumothorax as compiled from reports by Bezançon and others (4), Pissavy (5), Toinon (6), Rist and Veber (7), Unverricht and Dosquet (8), Mainini (9), Maendl (10), Bernard and Baron (11), Murard (12), Dumarest (13) and Rist and Naveau (14). They found 40 per cent of effusions occurring during the first two months of pneumothorax. The patients in our series have been under treatment from two to eight months. No cases of tuberculous or mixed-infection pyothorax have occurred in our series of cases so far.

The other complications were mild and caused neither great discomfort to the patient nor serious interference with treatment.

An observation which was contrary to our expectations was the tolerance of disproportionately larger amounts of air in relation to the frequency of refills. Some patients received refills of 300 to 400 cc. of air daily over periods of two or three weeks without marked discomfort, though a considerable degree of pulmonary collapse resulted. It is obvious that these patients could not have tolerated 2,100 or 2,800 cc.

of air weekly, or even half of these amounts semiweekly, without discomfort. Even if it is assumed that the rate of absorption of air increases in proportion to the frequency of its introduction, this would not suffice to explain this extreme variation in tolerance.

SUMMARY

During the six months from July, 1935, to January, 1936, inclusive, pneumothoraces were attempted for the collapse of 69 lungs in 65 patients. The lesions in these 69 lungs were in the proportion of 39 per cent Moderately Advanced and 60.9 per cent Far Advanced. Fifty-three operable pneumothoraces were obtained. These pneumothoraces were continued by the use of refills of such size and frequency as to obtain cavity closure as rapidly as possible by a uniformly progressive type of collapse of the diseased tissue. In 12, or 22.6 per cent, of these, pneumothorax was proved a *Therapeutic Failure* after trial for an average period of 4.8 weeks. In 35, or 66 per cent, a satisfactory collapse of the lung was obtained within an average period of 10.4 weeks. Complications encountered were at least no more frequent or serious than is the expectancy for any similar group of cases with any method of administering pneumothorax.

CONCLUSIONS

The use of pneumothorax refills of such size and frequency as to obtain cavity closure as rapidly as possible by a uniformly progressive type of collapse is desirable for scientific and economic reasons. Such a manner of administering pneumothorax apparently does not increase the incidence or seriousness of the complications of pneumothorax therapy.

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EMPHYSEMA OF THE ARTIFICIAL-PNEUMOTHORAX LUNG[1]

Vesicular, Subpleural, Interfascial

EPHRAIM KOROL[2]

In certain cases of artificial pneumothorax, the treated lung presents transparent areas which on the roentgenogram appear as bright or brighter than the air in the pneumothorax cavity. I am not aware that this phenomenon has heretofore been discussed in the English medical literature.

REVIEW OF THE LITERATURE

Cardis and Bourguinon (1) first discussed this subject in 1931. They described three cases. The pneumothorax was incomplete, and the partly collapsed lung was adherent anteriorly in each case. There was a serofibrinous effusion in two cases, a purulent exudate in the third case. The pneumothorax was gradually obliterated by contracting adhesions. The expanding lung was very radiolucent in contrast with the thickened pleura overlying the contiguous air-pocket. The authors do not mention emphysema as a factor, but they report that the breath-sounds were feeble over the adherent lung and that fluoroscopically the lung showed very little respiratory activity. These are signs of emphysema. One case was examined postmortem: the parietal pleura overlying the air-pocket was greatly thickened, much more so than the visceral pleura.

In October, 1931, G. Torelli (2) read a paper, entitled *The Opaque Pneumothorax*, before the National Tuberculosis Society, meeting in Bologna. He presented 12 cases of artificial pneumothorax of long standing. In ten of the cases there was an exudative pleuritis while under observation. The lung was incompletely collapsed, and there was an extensive pachypleuritis in each case which involved chiefly the parietal pleura. The "opaque pneumothorax" was caused by thickened parietal pleura. Several of Torelli's patients were examined with a thoracoscope: the majority of these showed thick layers of fibrin on the

[1] Presented at a session of the Clinical Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

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parietal pleura. It must be mentioned that in a few of his cases there was no endoscopic evidence of thickened pleura. It is reasonable to assume that in the latter cases the X-ray appearances were caused not so much by thickened pleura as by changes in the lung, that is, by emphysema.

In 1932 Torelli (3) described two more cases of opaque pneumothorax. Both cases had effusions and signs of bronchial fistula. The phenomenon was chiefly due to great thickening of the parietal pleura which rendered the pneumothorax cavity more radiopaque than the partly expanded lung. In one case the pleural thickening gradually extended to involve the visceral pleura and then the paradoxical transparencies disappeared.

Accorimboni in 1932 and 1933 (4) (5) discussed the paradoxical appearance of the lung in artificial pneumothorax complicated by adhesive pleuritis. He described 14 cases, all associated with pleural effusions of long duration. The partly collapsed lung was held to the chest-wall by adhesions. The pleurisy which followed the pneumothorax attacked the parietal pleura overlying the pneumothorax, but the visceral pleura was spared due to the preëxisting adhesions. There is a gradual opacification of the pneumothorax cavity in contrast with the collapsed lung which may undergo expansion. Emphysema is not mentioned as a possible factor in this X-ray appearance.

Saul (6) is interested principally in the lung changes, associated with increased air-content (that is, emphysema), which may produce increased transparencies on the roentgen film. He recognizes that the emphysema may be either intrapulmonary, or there may be a collection of air between the lung and its visceral pleura, or the air may penetrate the adherent lung and accumulate between strands of adhesions. His case histories and illustrations are very similar to the material of the preceding writers, but Saul lays emphasis on the areas of emphysema as cause of the paradoxical roentgenographic appearance while the associated pachypleuritis is not mentioned. In the one case in which there was a postmortem examination, the radiolucent lung was shown to consist of an adherent emphysematous anaemic middle lobe of the right lung.

DISCUSSION

In practically all cases described there was a pleural exudate of long duration. In the majority of cases there were signs of bronchial fistula, such as high pressures in the pneumothorax, purulent effusions rich in tubercle bacilli, or attacks of spontaneous pneumothorax. In all the

cases the lung collapse was incomplete due to adhesions which existed prior to the induction of the pneumothorax.

During attacks of pleurisy the parietal pleura undergoes great thickening, while the reaction of the visceral pleura is much milder. This difference in reaction of the two pleural membranes has been attributed to the peculiarities of the lymph drainage of the pleura (7). This relative inertness of the visceral pleura makes it possible for the lung to rëexpand after long periods of collapse and after severe attacks of pleurisy; for the same reason perforations through the visceral pleura are common, while it is very unusual for an empyema to point through the parietal pleura on to the chest-wall.

The thickened parietal pleura is largely responsible for the "opaque pneumothorax," while the transparency of the adherent lung is enhanced by the scant blood-supply of the poorly functioning adherent lung.

If the lung treated by artificial pneumothorax is incompletely collapsed due to adhesions, the tuberculous process often progresses steadily in the adherent lobules. When the lesions reach the lung periphery, there occur attacks of pleurisy with or without perforation into the pneumothorax cavity. The adherent lung lobules often undergo changes of obstructive emphysema, the supplying bronchioles being stenosed by caseous material or granulation tissue. The emphysema blebs gradually enlarge and may rupture into each other or through the visceral pleura. In case the visceral pleura is thickened, the lung parenchyma may be dissected away from the pleura for long distances. Should the emphysema bleb point in an area where the lung is adherent, instead of into the pneumothorax cavity, the air may penetrate and accumulate between strands of adhesions, and may cause subcutaneous and mediastinal emphysema.

If these areas of emphysema are situated near the outer aspect of the lung, adjacent to the pneumothorax, they will be easily demonstrable on the X-ray films, constituting the "bright spots" under discussion. If situated on the anterior or posterior aspect of the adherent lung these air accumulations generally escape detection unless large enough to be discovered by palpation (subcutaneous emphysema).

ILLUSTRATIVE CASES

1: World War veteran, 40 years of age. Artificial pneumothorax was induced in August, 1929. The lung could not be collapsed completely due to basal

adhesions. There was an attack of pleurisy with effusion during the spring of 1931 and another attack in the fall of that year. Early in 1933 the patient began to lose weight, his cough increased, and he had several small haemoptyses. The cough assumed a peculiar low and hollow quality which suggested a large bronchial fistula. The tubercle bacilli reappeared in the sputum. Fluid returned in the pleural cavity and persisted. Frequent aspirations of air or fluid were necessary to relieve pain and pressure. The anterior mediastinum was ballooned out, and on several occasions there was subcutaneous emphysema. During the numerous aspirations it was learned that the parietal pleura was gaining in thickness and toughness.

In August, 1934, the man began to improve. His cough decreased and lost its peculiar sonorous character. The need for aspirations became less frequent. The tubercle bacilli disappeared from the sputum, and he began to gain weight.

The roentgenogram of September 10, 1931 (figure 1) shows a large pneumothorax on the right side. The lower lobe is invisible. The collapsed upper lobe is seen opposite the 2nd-rib cartilage; it is separated from its visceral pleura by a collection of air—subpleural emphysema. The middle lobe is adherent. It shows much fibrosis and pleural thickening and several annular shadows representing emphysema blebs. The summit of the middle lobe is separated from its visceral pleura by a collection of air.

The film of November 1, 1932 (figure 2) shows fluid in the right pleural cavity, reaching the 7th cartilage. The pneumothorax is under pressure, to judge by the bulging interspaces, the increased transparency of the right chest, the collapse of the lung, and the displacement of the heart. There has appeared a line of thickened parietal pleura in the axilla. The middle lobe is atelectatic, it is separated from the visceral pleura throughout its length by subpleural emphysema.

The film of July 3, 1935, shows marked contraction of the right chest and marked increase in the pleural thickening. The right middle lobe has reexpanded and the subpleural emphysema has disappeared. There is a large emphysema bleb in the apex of the lobe.

Summary: In a case of incomplete pneumothorax, the tuberculous disease progressed in the adherent lung with a production of bullous emphysema. There was evidence of air burrowing through pleural adhesions (subcutaneous emphysema) and X-ray signs of subpleural emphysema. After progressive organization of the visceral pleura, the signs of the bronchial fistula disappeared; the subcutaneous emphysema and the subpleural emphysema disappeared as well.

2: World War veteran, 35 years of age. Artificial pneumothorax was induced on the right side in August, 1927. The lung was incompletely collapsed and

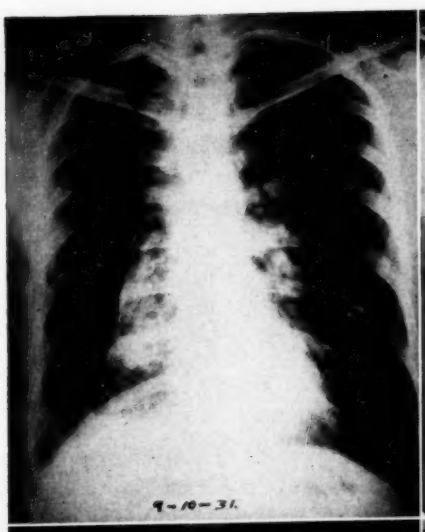

Fig. 1

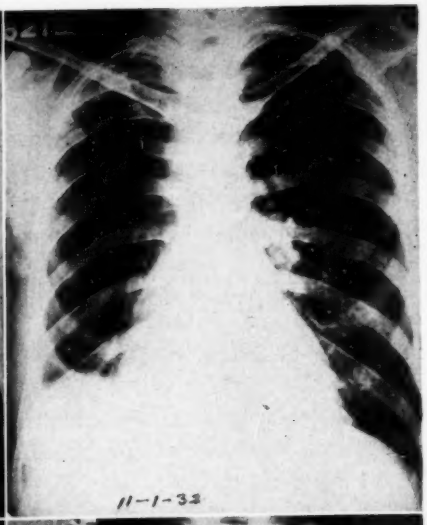

Fig. 2

Fig. 3

Fig. 5

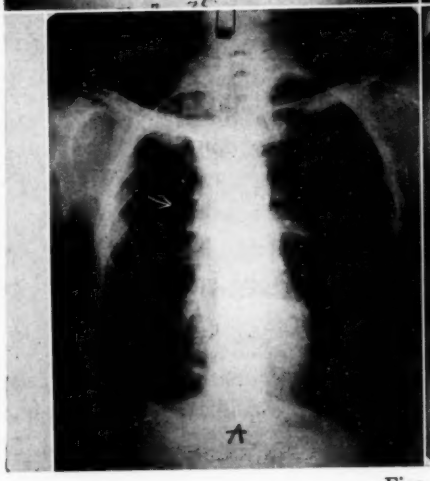

Fig. 4A

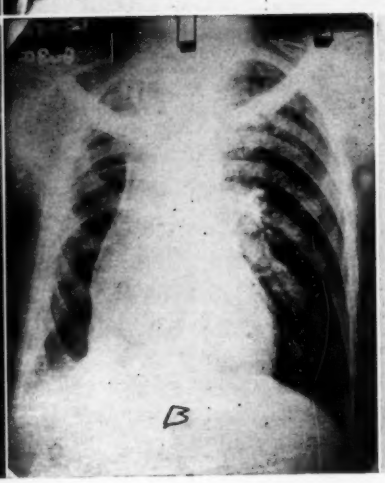

Fig. 4B

Figs. 1–5

there persisted a cavity in the right apex. During the spring of 1928 there was an attack of pleurisy; fluid developed in the pneumothorax and it never absorbed completely. The fluid caused pressure symptoms and required periodical aspirations. During the summer of 1932 the fluid became purulent and there was a septic type of fever. Oil of gomenol injected into the pneumothorax was soon expectorated. The disease later spread to the left lung. Postmortem, a large fistula was found connecting the apical cavity with the pneumothorax. The parietal pleura was very thick and hard, and there were firm interlobar adhesions. The partly collapsed right lung was adherent to the chest wall both anteriorly and posteriorly.

The roentgenogram dated August 24, 1931 (figure 4A) shows hydropneumothorax on the right side. There is the familiar line of thickened parietal pleura in the right axilla. The partly collapsed right lung is stripped from its visceral pleura through the greater extent of its lateral border, but a few bridges of tissue can be seen running from the lung to the pleura. Opposite the 6th vertebra a gap can be seen in the visceral pleura.

The film of December 13, 1932, (figure 4B) shows contraction of the right chest with progressive thickening of both the visceral and parietal pleura.

Fig. 1. The roentgenogram of September 10, 1931 (case 1) shows a large pneumothorax on the right side. The lower lobe is invisible. The collapsed upper lobe is seen opposite the 2nd-rib cartilage; it is separated from its visceral pleura by a collection of air,—subpleural emphysema. The middle lobe is adherent. It shows much fibrosis and pleural thickening and several annular shadows representing emphysema blebs. The summit of the middle lobe is separated from its visceral pleura by a collection of air.

Fig. 2. The film of November 1, 1932 (case 1) shows fluid in the right pleural cavity reaching the 7th cartilage. The pneumothorax is under pressure, to judge by the bulging interspaces, the increased transparency of the right chest, the collapse of the lung, and the displacement of the heart. There has appeared a line of thickened parietal pleura in the axilla. The middle lobe is atelectatic, and is separated from the visceral pleura throughout its length by subpleural emphysema.

Fig. 3. The film of July 3, 1935 (case 1) shows marked contraction of the right chest and marked increase in the pleural thickening. The right middle lobe has reëxpanded and the subpleural emphysema has disappeared. There is a large emphysema bleb in the apex of the lobe.

Fig. 4A. The roentgenogram, dated August 24, 1931 (case 2), shows hydropneumothorax on the right side. There is the familiar line of thickened parietal pleura in the right axilla. The partly collapsed right lung is stripped from its visceral pleura through the greater extent of its lateral border, but a few bridges of tissue can be seen running from the lung to the pleura. Opposite the 6th vertebra a gap can be seen in the visceral pleura.

Fig. 4B. The film of December 13, 1932 (case 2) shows contraction of the right chest with progressive thickening of both the visceral and parietal pleurae. The subpleural emphysema has disappeared. At the site of the previous break in the visceral pleura there is an area of great transparency, attributable to an accumulation of air between strands of adhesions.

Fig. 5. Case 3. Shows a large air-bubble of interfascial emphysema; also evidence of mediastinal emphysema.

The subpleural emphysema has disappeared. At the site of the previous break in the visceral pleura there is an area of great transparency, attributable to an accumulation of air between strands of adhesions.

Summary: In a case of incomplete pneumothorax with chronic pleural effusion there was subpleural emphysema with evidence of a break through the visceral pleura. After cicatrization and contraction of the pleural membranes, the subpleural emphysema disappeared.

3: Male, 40 years of age. Cavernous tuberculosis of left lung, developing acutely in November, 1934. Artificial pneumothorax, begun on December 12, 1934, was incomplete due to adhesions. Perforation of the cavity into the pneumothorax occurred on April 23, 1935, and there was high intrapleural pressure for several weeks, requiring numerous aspirations of air and fluid. There was a septic type of fever and much sputum containing tubercle bacilli. The pleural exudate was also rich in tubercle bacilli. The roentgenogram of June 24, 1935, shows a hydropneumothorax on the left side with the fluid level at the 4th-rib cartilage. The left lung is collapsed, with the exception of a slit-like cavity which is held open by an adhesion. There is an oval area of increased transparency in the 2nd interspace opposite the 7th rib, posteriorly, representing an accumulation of air in the tissue of the chest-wall; just inside of this air-bubble can be seen a less well-defined air collection protruding from the mediastinum. The film of July 29, 1935 (figure 5) shows the air-collections clearly.

Following open drainage on October 12, 1935, the man improved and the left lung began to expand. The tubercle bacilli disappeared from the sputum as well as from the pleural exudate. The interfascial emphysema also disappeared, and the air-bubbles were no longer visible during the examination of October 29, 1935.

Summary: In a case of high-pressure pneumothorax, there developed collections of air in the chest-wall and in the mediastinum. After the tuberculous process subsided and the lung began to expand, the interfascial emphysema disappeared.

CONCLUSIONS

In certain cases of artificial pneumothorax, there develop in the treated lung areas of great radiolucency, which on the roentgenogram may appear brighter than the air of the contiguous pneumothorax. This phenomenon is caused by the following factors: (1) a progressive pachypleuritis which thickens the pleura overlying the pneumothorax but spares the treated lung due to preëxistent adhesions; (2) areas of vicarious em-

physema in the adherent lung; (3) air-pockets between strands of adhesions or between the lung and the visceral pleura.

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EMPYEMA COMPLICATING ARTIFICIAL PNEUMOTHORAX[1,2]

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Tuberculous empyema or tuberculous empyema complicated by superimposed mixed infection are the most serious complications of pneumothorax therapy. These complications may make their appearance during any phase of the treatment, but characteristically, as most other complications, they are more apt to appear during its earlier months.

The clinical symptoms are very variable, ranging from the mild symptoms of the tolerated tuberculous empyema to the severe toxaemia of the patient with superimposed mixed-infection empyema.

The classification of empyema varies, but for clarity in discussion we wish to limit our classification to the two classes, tuberculous empyema and the tuberculous empyema with superimposed pyogenic infection.

INCIDENCE

The incidence of empyema complicating artificial-pneumothorax therapy has, of course, shown no absolute increase during recent years. There has, however, been a definite increase in the total number of cases, but this increase is only relative and is brought about by the greater number of patients undergoing pneumothorax therapy. About two years ago we made a survey of the clinical records of 750 patients who had been treated by induced pneumothorax over a period of four and one-half years and found the incidence of pneumopyothorax to be 5.8 per cent.

AETIOLOGY

The aetiological factors of empyema may be divided into three groups: (1) the unforseen and often unpreventable indirect accidents of pneumo-

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[2] Published by permission of the Surgeon General, U. S. Army, who is not responsible for any opinion or conclusion drawn herein.

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thorax therapy; (2) those factors more directly associated with the therapy but somewhat controllable by precautionary methods; and (3) those factors of neglect either on the part of the patient or physician.

The aetiological factors unforseen and of a more or less accidental character are those instances of superimposed spontaneous pneumothorax following the spontaneous rupture of subpleural ulcerative tubercles, subpleural emphysematous blebs or the rupture of smaller pleuropulmonary adhesions at their pulmonary attachment with resultant injury to the lung parenchyma.

Autopsy study has given conclusive evidence that, in the instances of spontaneous rupture of subpleural lesions, the most frequent site is near the pulmonary attachment of pleural adhesions. This may be explained by tension upon an area of lung tissue containing ulcerative tuberculous lesions, and this tension results in disease progression with spontaneous rupture through the visceral pleura. Though sufficient compression with relaxation of lung parenchyma may be obtained by the pneumothorax for healing elsewhere in the involved lung, this particular area of caseation at the base of an adhesion does not share the necessary conditions essential for healing. The pneumothorax, because of the presence of pleural adhesions with their counter traction, defeats the very purpose of the therapy. Smaller adhesions may rupture during coughing attacks or may follow physical effort of the patient without the use of positive intrapleural pressure. Gas as a foreign body may also set up a pleuritis.

Those factors more directly associated with the therapy are positive intrapleural pressure and rupture of larger pleural adhesions, or positive pressure, through its factor of greater variation from the normal physiological negative, acting as an irritant to the pleura containing tubercles. Intrapleural surgery, the use of intrapleural agents, as oil, for compression, and chest fistulae following aspirations for hydrothorax, may be responsible for an empyema.

Factors of neglect include errors of aseptic technique, neglected hydrothoraces and sudden discontinuance of pneumothorax with considerable pulmonary compression without attention to the details essential to proper pulmonary reëxpansion.

As stated, our incidence of pneumopyothorax in 750 pneumothorax patients was 5.8 per cent. Of 35 patients with tuberculous empyema, 21, or 60 per cent, were preceded by a superimposed spontaneous pneumothorax and 14, or 40 per cent, developed from clear fluid in the absence of a demonstrable spontaneous pneumothorax.

The above figures show that the majority of pneumopyothoraces, at least in our series, follow superimposed spontaneous pneumothorax. Not all instances of this complication, however, are followed by severe complications, for in our series, 13.4 per cent of patients undergoing pneumothorax therapy had at some time during the treatment the complication of spontaneous pneumothorax. This figure is rather high, and we believe that it is explained by the fact that in our hospital pneumothorax patients are fluoroscoped before and after each pneumothorax refill. By this observation rather slight to moderate examples of spontaneous pneumothorax are detected which would otherwise have been missed. In patients who have suffered this complication, a certain percentage develop exudation, and of these a certain per cent develop pyothorax. Whether or not the latter condition develops rather depends upon the size and duration of the bronchopleural fistula. Smaller fistulae, which readily close because of the increase in pulmonary compression, are not likely to be followed by further complications.

In a series of 45 patients who definitely had a superimposed spontaneous pneumothorax during the past two years, only 10, or 22.7 per cent, developed a purulent exudate subsequent to the complication. Larger fistulae, which remain patent over an extended period, usually develop pyothorax. No definite interval of patency of the fistula can be stated as being sufficient to always produce pyothorax. During the past year we have treated two patients with open pleurobronchial fistula, which required a retention needle with water-valve for pneumothorax decompression, one for a period of 10 days and another for a period of 14 days, yet neither patient subsequently developed empyema.

In superimposed spontaneous pneumothoraces with open fistula, the pleural exudate formed is usually serofibrinous in character, but it soon becomes cloudy, and eventually the exudate is definitely purulent in type and contains the various microörganisms common to the respiratory tract. Secondary infection is rather unavoidable, since we are dealing with a direct communication between the respiratory tract and the pleural space.

In the past three years, in our series of 36 patients who developed pneumopyothorax following spontaneous pneumothorax, 26 patients presented a patent fistula requiring pneumothorax decompression over a period of time ranging from 2 to 10 days.

In smaller fistulae which remain open only for a short time, say 24

to 48 hours, an exudate may form, but with proper care, as a rule, this does not become purulent. If unaspirated or if the exudate is not aspirated frequently, a great many become purulent and the vast majority of these are tuberculous without secondary invaders. The spontaneous rupture of a parenchymal lesion through the visceral pleura into the intrapleural space results in the infection of the space by tubercle bacilli and, if the tubercle bacilli are allowed to remain in the pleural exudate at body temperature for a long period, the exudate will in time become purulent. We believe this may be prevented by keeping the pleural space relatively dry by repeated aspiration. Occasionally infection has been rather extensive and a purulent exudate forms even though every phase of therapy is utilized to prevent the complication.

During the past two and one-half years we have treated 250 patients who presented initially a serofibrinous exudate of clinical significance, and of these patients, 59, or 23.6 per cent, developed an exudate of purulent character.

As stated, a neglected clear exudate may in time become purulent, even without the accident of spontaneous pneumothorax. We have observed this complication in patients who have abandoned the hospital, with a satisfactory pneumothorax, but who have failed to continue their pneumothorax refills. Air is absorbed from the pleural space more rapidly than pulmonary reëxpansion can be accomplished, high negative pressure results, and the so-called "dead space" is filled by exudation. Often the pleura loses somewhat its permeability and the exudate is spontaneously resorbed slowly or not at all. Continued neglect of treatment in these cases may result in the formation of a purulent exudate. Treatment is difficult in this particular type of case because the pleura tends to be so extremely thickened that pulmonary reëxpansion, to aid therapy by obliteration of the empyema pocket, is next to impossible.

Though the introduction of pyogenic organisms during pneumothorax refills and during thoracentesis, for removal of serofibrinous exudations, is given as an aetiological factor of pyothorax, we can cite no patient in our series in whom this was the exciting cause. Strict aseptic technique should prevent the introduction of pyogenic organisms during routine surgical procedures.

Intrapleural surgical procedures, especially intrapleural pneumolysis with cauterization of adhesions, may be followed by pneumopyothorax.

The pleural exudate following intrapleural pneumolysis is usually serofibrinous initially but may rapidly become purulent. This procedure has accounted for four of our pyothoraces.

In a series of 24 patients with a tuberculous empyema complicated by superimposed mixed infection, spontaneous pneumothorax was attributed to be the causative factor in 15, or 62.5 per cent, of cases; 4, or 16.7 per cent, followed intrapleural surgical procedures; 4, or 16.7 per cent, followed pleurocutaneous fistula in the treatment of tuberculous empyema; and 1, or 4.1 per cent, occurred following thoracoplasty.

TREATMENT OF EMPYEMA COMPLICATING ARTIFICIAL PNEUMOTHORAX

We concur in the opinion of Alexander that "It is impossible to prepare a simple formula that can be applied to the treatment of all cases of tuberculous empyema. Attempts to standardize rather than individualize treatment are chiefly responsible for the high mortality of the disease."

Tuberculous empyema complicating artificial pneumothorax is treated at our institution by oleothorax in combination with other surgical and medical procedures according to definite indications. We use paraffine oil or *Mazola*, to which 5 or 10 per cent gomenol has been added, the technique having been originally adopted from the Matson Clinic.

After aspiration and complete removal of the pus, the pleural cavity is thoroughly irrigated with saline solution. The oil injection is made with the patient in the pneumothorax-refill position. Air is withdrawn after each injection of 25 to 50 cc. of oil, to avoid excessive disturbance of the intrathoracic equilibrium. The oil injected is massive and sufficient to bathe the entire surface of the serosa. A 3-inch, 13-gauge needle with a one-way stop-cock is used in pyothorax cases. This type of needle permits aspirations, irrigation and instillation under negative intrapleural pressure. The maintenance of a negative intrapleural pressure is absolutely essential to obtain pulmonary reëxpansion and obliteration of the empyema pocket in certain cases. Aspirations are repeated as often as is necessary to keep the hemithorax relatively free from exudate.

In spite of diligent treatment, a certain percentage of empyema cases fail to respond to oleothorax therapy. In some cases the infected pleura is so thick that the oil is not permitted to exert its influence upon the deeper-lying infected structures.

In attempting to treat empyema complicating artificial pneumothorax we believe it is essential to formulate a definite plan of procedure from the

start. This plan must be individualized and remain flexible, allowing for alternatives in the event of failure to respond to the initial procedures. The plan of treatment will depend on (1) the nature of the empyema, whether tuberculous or complicated by secondary infection; (2) the extent and nature of the pulmonary involvement; and (3) the symptoms and general condition of the patient.

The tuberculous-empyema patients are treated by gomenol in oil. Whether or not an attempt is made to reëxpand the lung depends on the following: (1) The extent of the pulmonary involvement and the activity of the lesions in the two lungs; (2) the response of the empyema to gomenol therapy; (3) the presence or absence of pleurocutaneous or pleuropulmonary fistula; and (4) the severity of the symptoms as to tolerance of the empyema.

If the pulmonary lesions are arrested in tuberculous empyema, gomenolized oil is introduced as a disinfecting medium. The pleural space is left with a high negative pressure following aspiration, irrigation and instillation, in an attempt to draw the compressed lung out to the chest-wall and thus obliterate the empyema pocket.

If active involvement is present, limited to the upper lobe, with or without patent cavities, an attempt is made to reëxpand the lung with a view to upper-stage thoracoplasty after the empyema is cleared up.

It is not considered advisable to continue compression of the lung by oleothorax over an extended period of time in upper-lobe involvement. The oleothorax tends to compress the lower lobe more than the upper lobe, and the presence of pus over an extended period of time will cause a pulmonary fibrosis and thickening of the visceral pleura, making reëxpansion difficult and impossible at a later date. Then, too, if the lung is maintained compressed over an extended period of time and if the pus fails to clear up, a complete thoracoplasty may be necessary to obliterate or greatly reduce the empyema space, whereas only an upper stage would have been necessary for the pulmonary tuberculosis had the lung been reëxpanded.

If active involvement is present in the entire lung, oleothorax is continued and pneumothorax maintained. If the empyema clears up, oleothorax may be discontinued and pneumothorax maintained. If, on the other hand, the empyema does not respond to treatment over an extended period of time, the only alternative is complete thoracoplasty to obliterate the empyema space and compress the diseased upper and lower lobes.

If active involvement is primarily in the lower lobes, oleothorax is continued with no attempt to reëxpand. The oil, in addition to acting as a disinfecting medium, also maintains compression of the lower lobe and may allow the upper lobe to reëxpand, depending on the quantity of oil left in the pleural space. If the oleothorax does not clear up the empyema over an extended period of time, a lower-stage thoracoplasty may be accomplished to obliterate the empyema space and maintain compression of the diseased lower lobe. If the empyema clears up under treatment, the oil may be removed and replaced by air or the oil may be left in, converting the disinfection oleothorax into an inhibition or compression oleothorax.

Results of treatment in tuberculous empyema

	per cent	
Aspiration, irrigation and oleothorax alone, 18 cases	51.4	total cured, 57.1 per cent
Thoracoplasty required in addition to aspiration, irrigation and oleothorax, 2 cases	5.7	
Cases still under treatment and improved, 7 cases	20.0	
Dead, 8 cases	22.9	
Total, 35 cases	100	

The number of aspirations required in those cases that were cured ranged from 4 to 65. The average was 23. Eleven cases required less than 15 aspirations and 7 cases required between 20 and 65 aspirations to cure the empyema. The majority required between 12 and 16 aspirations.

The appearance of a mixed-infection empyema during the course of artificial pneumothorax treatment is necessarily alarming.

In these cases we attempt to eliminate the pyogenic organisms by irrigation and the instillation of various bacteriostatic dye preparations. The pleural space is left with a high negative pressure, in certain cases, in an attempt to rapidly reëxpand the lung and obliterate the empyema pocket. We have employed various substances for this purpose, none of which has proved consistently satisfactory. A 1:5,000 aqueous solution of gentian-violet or crystal-violet, a purer form of the same substance, has given the best results. The pyogenic organisms have been eliminated in a certain proportion of cases, and in other cases the violent nature of the infection has been controlled sufficiently to allow us to proceed with the obliteration of the pleural space. The anaerobic organisms are more resistant to this form of treatment than are the ordinary pyogenic ones; and, in the presence of a persistent pleuropulmonary fistula, it has not been possible to render the exudate sterile because of the constant reinfection from the focus within the lung.

The procedure in these cases is to aspirate at first daily, increasing the interval as the condition improves. After aspiration, the pleural space is irrigated thoroughly with saline solution or gentian-violet, and some of the dye is allowed to remain until the next aspiration.

In those patients in which a pleurobronchial or pleurocutaneous fistula is not patent, an attempt is made to obliterate the empyema pocket by pulmonary reëxpansion, using a high negative pressure. In the majority, however, pulmonary reëxpansion is obviously impossible. If the pleuropulmonary fistula remains patent and it is impossible to control the septic manifestations promptly, closed tube drainage may be instituted.

After the pyogenic infection has been controlled, an extrapleural thoracoplasty is usually necessary to obliterate the pleural cavity. The extrapleural thoracoplasty is performed in several stages, and a few ribs, only, are removed at any one time. Paralysis of the diaphragm, following division of the phrenic nerve, will at times aid in obliterating those empyema cavities situated near the diaphragm. Unroofing of the empyema cavity is not done unless extrapleural thoracoplasty has failed to completely obliterate the space. If the capacity of the pocket is less than 300 cc. an unroofing may be considered. If larger than 300 cc., further compression is necessary before an unroofing should be considered.

Results of treatment in secondarily infected empyema

	per cent
Cured, 5 cases	20.8
Living but worse, 2 cases	8.3
Dead, 17 cases	70.9
Total, 24 cases	100

The five cases now living and cured required a complete extrapleural thoracoplasty. Unroofing was necessary in four cases, and it may be necessary in the fifth case, as the patient still has a 200-cc. pocket of clear fluid that requires aspiration every two weeks.

SUMMARY OF RESULTS

1. In a series of 750 patients treated by pneumothorax over a period of four and one-half years, empyema occurred as a complication in 5.8 per cent of cases.

2. In the 35 cases of tuberculous empyema, spontaneous pneumothorax was attributed to be the causative factor in 60 per cent of cases, while 40 per cent developed from clear fluid in the absence of a demonstrable superimposed spontaneous pneumothorax.

3. In the 24 patients with a mixed-infection empyema, spontaneous pneumothorax was attributed to be the causative factor in 15, or 62.5 per cent, of cases; 4, or 16.7 per cent, followed intrapleural surgical procedures; 4, or 16.7 per cent, followed pleurocutaneous fistula in the treatment of tuberculous empyema; and 1, or 4.1 per cent, occurred following thoracoplasty.

4. Superimposed spontaneous pneumothorax occurred as a complication in 13.4 per cent of 750 cases on pneumothorax therapy.

5. In a series of 45 patients who definitely had a superimposed spontaneous pneumothorax, 10, or 22.7 per cent, developed purulent exudate.

6. Of 36 patients who developed an empyema following superimposed spontaneous pneumothorax, 26, or 72.2 per cent, presented a patent pleurobronchial fistula, requiring pneumothorax decompression over a period of time ranging from 2 to 10 days.

7. Of 250 patients who presented initially a serofibrinous exudate of clinical significance, 59, or 23.6 per cent, developed exudate of a purulent character.

8. Of the 35 cases of tuberculous empyema, 20, or 57.1 per cent, were cured; 7, or 20 per cent, are still under treatment and improved; and 8, or 22.9 per cent, are dead. Oleothorax alone was used in curing 18, or 51.4 per cent of cases, and thoracoplasty in addition to oleothorax was required in 2, or 5.7 per cent of the cases.

9. Of the 24 cases of tuberculous empyema complicated by secondary infection, 5, or 20.8 per cent, are cured, 2, or 8.3 per cent, are living but worse, and 17, or 70.9 per cent, are dead. All 5 cases that were cured required a complete extrapleural thoracoplasty followed by unroofing in 4 cases.

CONCLUSIONS

1. Empyema is the most serious complication of therapeutic pneumothorax.

2. Every effort should be utilized to prevent this complication by attention to the aetiological factors.

3. With each empyema patient it is essential to formulate a definite plan of procedure from the start. This plan must be individualized and remain flexible, allowing for alternatives in the event of failure to respond to initial procedures. This plan must take into consideration, not only the empyema, but the pulmonary condition as well.

4. The use of gomenol in tuberculous empyema, and gentian-violet solution in the mixed-infection type, in conjunction with thoracoplasty when indicated, has proved satisfactory in a large per cent of cases.

Note: The authors wish to acknowledge their indebtedness to Dr. William C. Pollock for his valuable advice and assistance.

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TUBERCULOUS EFFUSIONS COMPLICATING ARTIFICIAL PNEUMOTHORAX[1]

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Tuberculous empyema following the induction of artificial pneumothorax in the treatment of pulmonary tuberculosis should always be looked upon as a serious complication and demands our every effort, not only to prevent its development, if possible, but to treat it by means of the most effective method or methods at our disposal.

With these thoughts in mind, we have made a study of all cases in a ten-year period which developed pleural effusions as a sequel to artificial pneumothorax to determine, if possible, the types of cases in which it most frequently occurred, and the factors which were directly or indirectly responsible for its occurrence. Our object also has been to show whether these factors which are apparently responsible for the development of fluid might not also directly or indirectly affect the success or failure of the treatment in question. Four methods of treatment will be discussed, and the merits of each will be evaluated.

In the tables the cases are divided into two main groups according to whether mechanical aid, such as aspiration or irrigation, was necessary or not in the course of treatment. In the first group are included 155 patients who had small amounts of serous exudates, all of which were transitory and all of which cleared without mechanical aid. The second group comprises 163 cases with serous and purulent exudates, all of which required mechanical aid in the course of treatment. Results will be recorded separately in the two groups.

In table 1 the cases have been classified according to the types of fluid present, namely, serous, seropurulent, and purulent. They have been further divided into four groups according to the method of specific treatment employed, namely (1) those in which no mechanical aid was required, (2) those receiving routine aspiration alone, (3) those in which various dyes were used in addition to aspiration, and (4) those treated by means of merthiolate irrigations. Immediate results so far as the

[1] An elaboration of an X-ray exhibit presented at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 22–25, 1936.

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effusions *per se* are concerned are given in table 1. Subsequent and ultimate results in all treated groups will be found in table 2.

During the past ten years ending in October, 1935, artificial pneumothorax has been established and refills subsequently given in 530 patients under treatment at the Waverley Hills Sanatorium. Of this number 446, or 84.0 per cent, had bilateral pulmonary tuberculosis as shown on X-ray, and 84, or 16.0 per cent, had unilateral disease. Almost all of the bilateral cases were in the far-advanced group and, in general, had a more intensive and longer-standing disease than the unilateral cases, most of which were moderately advanced. Of the 530 pneumothorax cases 343, or 65 per cent, were classified as having a satisfactory collapse, whereas 187, or 35 per cent, had an unsatisfactory collapse. Collapse of the lung was considered to be unsatisfactory when adhesions between the visceral and parietal pleurae prevented the collapse of cavities, or otherwise prevented the necessary immobilization of the lung through partial or incomplete collapse in noncavity cases. When the lung was unsatisfactorily collapsed, adhesions were responsible in practically all cases.

In a series of 151 pneumothorax cases reported by Hayes, 93, or 61.5 per cent, developed a serous effusion. Of these, 32, or 34.4 per cent, later developed an empyema. Of the 530 cases in our series, 318, or 60 per cent, were found to have either serous or purulent effusions at the time this study was made. After deducting those patients treated by mechanical means, the satisfactorily collapsed cases in the first group of 155 comprise 41 per cent of all satisfactorily collapsed cases in the series. Similarly, the unsatisfactorily collapsed cases with effusions in this group comprise 44 per cent of all the unsatisfactorily collapsed cases in the series. After deducting the 155 cases in the first group from the total of 530, it is found that of the mechanically treated cases only 91, or 38 per cent, of the satisfactorily collapsed cases developed effusions, as compared with 72, or 53 per cent, in the unsatisfactorily collapsed group. The significance of these findings in the two groups of cases will be discussed in detail presently.

All effusions in this series are considered definitely tuberculous in nature since they developed following the collapse of tuberculous lungs. Hedblom states, "The tuberculous nature of an empyema that follows therapeutic pneumothorax for pulmonary tuberculosis so proved seems to be generally assumed without question, whether or not it is preceded by a serous effusion." Practically all of the effusions in this series have

TABLE 1

TREATMENT	NUMBER OF CASES	TYPE OF FLUID	DEGREE OF COLLAPSE	CLEARED	IMPROVED	UNIMPROVED	LENGTH OF TREATMENT
Routine sanatorium care alone	155	Serous	Satisfactory, 104 Unsatisfactory, 51	104 (100%) 51 (100%)			
		Grand total	Satisfactory and unsatisfactory, 155	155 (100%)			
Aspiration alone	38	Serous	Satisfactory, 27 Unsatisfactory, 11	21 (77.8) 3 (27.3)	3 (11.1) 3 (27.3)	3 (11.1) 5 (45.4)	
	37	Seropurulent	Satisfactory, 22 Unsatisfactory, 15	16 (72.7) 5 (33.3)	0 1 (6.6)	6 (27.3) 9 (60.0)	
	25	Purulent	Satisfactory, 6 Unsatisfactory, 19	2 (33.3) 4 (21.5)	2 (33.3) 1 (4.8)	2 (33.3) 14 (73.7)	
							average
	100	Total	Satisfactory, 55 Unsatisfactory, 45	39 (70.9) 12 (26.7)	5 (9.1) 5 (11.1)	11 (20.0) 28 (62.2)	1 month—7 months—48 months 1 month—5 months—20 months
	100	Total	Satisfactory and unsatisfactory, 100	51 (51.0)	10 (10.0)	39 (39.0)	
Aspiration plus dyes	2	Seropurulent	Satisfactory, 0 Unsatisfactory, 2			2 (100.0)	
	33	Purulent	Satisfactory, 13 Unsatisfactory, 20	7 (53.8) 4 (20.0)	1 (7.7) 0	5 (38.5) 16 (80.0)	
							average
	35	Total	Satisfactory, 13 Unsatisfactory, 22	7 (53.9) 4 (18.2)	1 (7.6) 0	5 (38.5) 18 (81.8)	2 months—10 months—13 months 1 month — 7 months—42 months
	35	Total	Satisfactory and unsatisfactory, 35	11 (31.4)	1 (2.9)	23 (65.7)	

		unsatisfactory, 35	11 (31.4)	1 (2.9)	23 (65.7)	

Merthiolate irrigations	1	Serous	Satisfactory, 1 Unsatisfactory, 0	1 (100.0) 0			
	8	Seropurulent	Satisfactory, 7 Unsatisfactory, 1	5 (71.4) 0	2 (28.6) 1 (100.0)		
	19	Purulent	Satisfactory, 15 Unsatisfactory, 4	10 (66.6) 2 (50.0)	5 (33.4) 2 (50.0)		
	28	Total	Satisfactory, 23 Unsatisfactory, 5	16 (70.0) 2 (40.0)	7 (30.0) 3 (60.0)		average 1 month —7 months—24 months 4 months—8 months—12 months
	28	Total	Satisfactory and unsatisfactory, 28	18 (64.3)	10 (35.7)		
Total of mechanically treated cases	163	Grand total	Satisfactory, 91 (56%) Unsatisfactory, 72 (44%)	62 (68.1) 18 (25.0)	13 (14.3) 8 (11.1)	16 (17.6) 46 (63.9)	
	163	Grand total	Satisfactory and unsatisfactory, 163	80 (49.1)	21 (12.9)	62 (38.0)	

been examined by direct smear for tubercle bacilli and secondary microorganisms, and many have been cultured. Since the beginning of 1932, all fluids have been examined by direct smear and culture. In addition to this, guinea-pig inoculations have been made in all cases in which direct smear was negative for tubercle bacilli. Of the 28 fluid cases treated with merthiolate irrigations since the beginning of 1932 (table 1), all were proved positive for tubercle bacilli, either by direct smear or guinea-pig inoculation. This would tend to prove that effusions developing subsequent to the collapse of tuberculous lungs are not only always tuberculous in nature but that tubercle bacilli can be found in nearly every case if the proper procedure of examination is followed. Only five of the 318 cases, or 1.5 per cent, were found to be secondarily infected. The organisms found were the staphylococcus and streptococcus. It is felt that a superimposed secondary infection in these cases should be rare when the best technical skill is assured.

In analyzing our tables there appear to be two chief factors which apparently are responsible in part at least for the development of effusions following the institution of artificial pneumothorax. The first of these factors, in the absence of active disease of the pleura, is thought to be chiefly mechanical; the other, the result of an exudative pleuritis due to active disease within the lung and pleura. The exudative pleuritis in this group of cases is thought for the most part to be dependent upon a similar active pathological process within the lung which has extended directly or by way of the lymphatics to the pleura. The presence of these two factors appears even more directly to affect the success or failure of the treatment so far as the fluids *per se* are concerned. Particularly is this true when mechanical aid, such as aspiration or irrigation, is necessary in the treatment, and most important of all in this latter group of active pleuritis cases when the collapse of the lung is satisfactory or unsatisfactory. When the fluid-formation is due purely to mechanical irritation in the absence of an active or exudative pleuritis, one would expect the fluid to be serous in character rather than purulent. Too, the amount of fluid formed would be small and transitory, and one would expect complete clearing to take place without mechanical intervention. Such was found to be the case in the first group of 155 patients. When the fluid is formed as a result of an exudative pleuritis, one might expect exacerbations at times due to mechanical intervention. Most important still, when the collapse of the lung is unsatisfactory in such cases, one would expect the exudative pleuritis to be progressive,

due to the inability to put at rest (by proper collapse) the active disease within the lung. For this reason one might expect aspiration or irrigation to be of little avail in these unsatisfactorily collapsed cases. Such has been the case in the second group of 163 patients.

At the time of this writing it is our opinion that the use of positive pressures in artificial pneumothorax plays little part in the production of effusions. Another member of the staff, however, is working on this problem from a statistical standpoint and will publish his data in a separate paper.

In most cases of pulmonary tuberculosis, pleuritis is no doubt a result of direct extension of the pulmonary process to the pleura or extension through the pulmonary lymphatics. The path of lymphatic extension to the pleura was demonstrated by William Snow Miller, who showed that there are valves opening toward the pleura between the deep venous and superficial subpleural lymphatics. Like the pulmonary lesion, the tuberculous pleuritis may be productive or exudative. Sauerbruch makes the statement that the type of pulmonary lesion is indicated by that of the pleuritis. Therefore, in the predominantly productive types of pulmonary tuberculosis one would not expect a pleuritis of an exudative character. We believe that the first 155 cases in our series might largely fall into such a classification. At least we do not believe that these cases for the most part had an active exudative pleuritis. It is felt that the development of the effusions in these cases and the fact that the effusions were simple serous exudates, which cleared within a relatively short period of time without mechanical aid, had no relation to the success or failure of the collapse of the lung. In this group it has already been pointed out above that 41.2 per cent of the satisfactorily collapsed cases developed fluid and 44.3 per cent or practically the same percentage of unsatisfactorily collapsed cases developed fluid. It is believed that the effusions in these cases were due in most instances to mechanical irritation of a relatively inactive pleuritis. The most common example of such irritation is the air in the pleural cavity. Possibly in other cases, irritation by the aspirating needle or, more likely still, the peeling away of small fibrinous strands between the surfaces of the pleurae might result in the development of a small amount of nonmalignant exudate. For this reason small effusions in such cases, regardless of whether the lung was satisfactorily collapsed or not, would be nonprogressive and would be expected to clear without mechanical interference.

However, it is believed that the remaining 163 cases which required

mechanical aid in their treatment should be placed in a different category from the above group of cases just discussed. Here it is felt in the majority of instances that, since the effusions are progressive and resistant to treatment, we are dealing with an active exudative pleuritis. In some of these cases also it is felt that the exudative process may be stimulated to increased activity by an aspirating needle or an irrigating fluid or other secondary mechanical influences. Too, it is felt that some of the dyes previously used in the treatment of empyemata may have irritated and therefore stimulated the development of pus rather than retarded it. This might be inferred from the results in our dye group as compared with the other groups. In general, however, in this whole group of 163 cases the immediate results of treatment have been comparatively favorable when the lungs were satisfactorily collapsed, and distinctly unfavorable when the collapse was unsatisfactory. It is reasonable to assume that in the latter group the pleuritis remained active and progressive because the pathological process within the lung remained active and progressive. This reasoning appears to be logical in view of the fact that 53 per cent of the unsatisfactorily collapsed cases in this group developed effusions, whereas only 38 per cent of the satisfactorily collapsed cases developed effusions. The fact that the process within the unsatisfactorily collapsed lung remains active makes for a greater opportunity for the development of fluid, since the pleuritis remains active and exudative. When the lung is put at rest, however, a productive tuberculosis is more likely to develop within the lung and pleura, replacing to a large extent the exudative character of the lesion.

If for no other reason than this, when the collapse of the lung remains unsatisfactory, an early discontinuance of artificial pneumothorax should be urged and a more appropriate form of collapse therapy should be substituted when indicated. Thoracoplasty is usually the method of choice. This holds true when intrapleural pneumolysis cannot be successfully performed, or in some selected cases when phrenicectomy fails to aid the pneumothorax in properly collapsing the lung.

The immediate results of treatment so far as the effusions are concerned in the 163 cases classified as having an active progressive exudative pleuritis, and therefore requiring active mechanical aid in the course of treatment, are to be found in table 1.

An attempt has been made to evaluate these results; and, as has already been pointed out, when the collapse of the lung was satisfactory, results were comparatively good, and, where the collapse was unsatisfactory,

results were uniformly poor regardless of the method of treatment used. Immediate results in the merthiolate group, however, in both the satisfactorily and unsatisfactorily collapsed cases were more favorable than in the groups in which simple aspiration alone was resorted to or dyes were used. In the merthiolate group all cases were classified as having completely cleared or as having shown improvement, so far as the effusions are concerned following their course of treatment. When the collapse of the lung was satisfactory, 70 per cent of the cases cleared completely and 30 per cent were improved. In the aspiration group 70.9 per cent of the satisfactorily collapsed cases cleared, 9.1 per cent improved and 20.0 per cent remained unimproved. The high percentage of cases which cleared in this group is due to the large number of serous exudates included in the group. Considering the pus cases alone, as shown in the table, more favorable results were obtained in the merthiolate group. In the dye group, 53.9 per cent of the satisfactorily collapsed cases cleared, 7.6 per cent improved, and 38.5 per cent remained unimproved.

When the collapse of the lung was unsatisfactory, the immediate results following treatment by the various methods were as follows: merthiolate group, cleared 40 per cent, improved 60 per cent; aspiration group, cleared 26.7 per cent, improved 11.1 per cent, unimproved 62.2 per cent; dye group, cleared 18.2 per cent, unimproved 81.8 per cent.

It will be seen in the table also that results were more favorable when the effusions were serous than when they were seropurulent or purulent.

Effusions recurred in the three treatment groups in about equal percentages. The fact that there were just as many recurrences in the merthiolate group, however, does not in any way detract from this method of treatment. In fact, we feel that the greater number of cases maintaining their collapse in the merthiolate group, as compared with the other treatment groups, makes for a greater chance of recurrence of effusions in the merthiolate group. Too, the much larger percentage of deaths in the aspiration group and dye group allows for fewer cases in which recurrence might take place in these groups. In fact, we believe we would have a larger percentage of recurrences in the aspiration and dye groups if they had maintained their collapses over a longer period of time.

Again, it is believed that after an effusion, due to an active exudative pleuritis, has cleared completely by a certain method of treatment, the chances for development of another effusion in these cases may be just

as great as it would be for the development for the first time of an effusion in any artificial-pneumothorax case.

Five cases in the merthiolate group had recurrences of their effusions. Recurrence in one took place after ten months. The effusion is now serous in character and small in amount, and there has been no active intervention since its return. Another patient had recurrence after ten months and is now improving under merthiolate irrigations. Two cases after six months and twelve months, respectively, redeveloped effusions. Oleothorax was resorted to in these cases, not primarily for their effusions, but to prevent reëxpansion of their lungs. Finally, there was one other patient after having been clear of fluid for seven months who redeveloped it, but soon afterward died of progressive pulmonary disease.

Thus far, we have discussed the relative value of the three methods of treatment, namely, routine aspiration alone, aspiration combined with various dyes, and merthiolate irrigations. The results discussed have reference only to the effusions themselves, and have not taken into consideration subsequent and ultimate outcome of the cases. These results are recorded in table 2. The cases are again classified into four treatment groups as in table 1, and are divided according to whether the effusions were serous, seropurulent, or purulent, and according to whether the collapse of the lung was satisfactory or unsatisfactory.

In the table will be found the number and percentage of cases in the different groups that have been able to continue their pneumothorax treatments to the present time, the number in which treatments were discontinued and the lungs allowed to reëxpand, those which were subsequently given oleothorax and thoracoplasty and, finally, those who died. The most outstanding finding in the table to our minds is the high percentage of deaths among those patients whose lungs were unsatisfactorily collapsed and the relatively few who died among those with successful collapse of the lung. Too, the percentage of deaths was not greatly influenced by the method of treatment employed, namely, routine sanatorium care, routine aspiration, aspiration plus dyes, or merthiolate irrigations; nor was there a greater percentage of deaths among the empyema cases than among those with serous exudates. It is felt that one can safely conclude that death in cases of pulmonary tuberculosis, complicated with effusions developing subsequently to artificial pneumothorax, is most frequently due to progressive pulmonary disease when the lung is unsatisfactorily collapsed. It is further believed that the effusions in these cases remain progressive rather than transitory, be-

cause the disease in the lung is active and progressive, and in such cases a serous exudate is more likely eventually to become purulent. That the effusions *per se* play only a minor rôle in causing death in the entire series is borne out by the fact that, in the first group of 155 patients who had only serous exudates which cleared completely, 70 per cent of the unsatisfactorily collapsed cases eventually died of progressive pulmonary disease. In fact, a larger percentage of deaths occurred among those patients with serous exudates than occurred among those with empyema.

We feel, therefore, that when the lung remains unsatisfactorily collapsed and one is convinced that continuation of artificial pneumothorax will not achieve its purpose, the collapse should be immediately discontinued. Many times it is difficult to decide this question, for the reason that the patient has temporarily improved both objectively and subjectively and the decision is indefinitely delayed. From our data it must be concluded that to temporize is to eventually increase not only the number of empyema cases but also the mortality rate. The increase in mortality rate applies not only to patients with effusions but equally as well to those without effusions. The important point is to discontinue an artificial pneumothorax which is not satisfactory, and substitute it in the great majority of cases with thoracoplasty. The earlier this is done the greater the number of lives that will be saved.

We definitely feel, however, that in those empyema cases in which satisfactory collapse has been accomplished, merthiolate irrigations, carried out according to the following technique, will in the great majority of cases effect a clearing of the empyema and allow for maintenance of the artificial pneumothorax.

The pus is removed by direct aspiration and the pleural cavity is irrigated at weekly intervals with merthiolate solution, 1–10,000, or 1–5,000, in normal saline solution, until the return is clear. Twenty to 100 cc. of the solution are left in the pleural cavity, and the intrapleural pressures are equalized following the treatment. As much as 200 to 300 cc. of the solution have been left in the pleural cavity in some instances. Soon after starting the treatment, the character of the pus becomes thin and assumes a light brownish color before finally disappearing.

In our merthiolate series 87 per cent are maintaining their collapse. As already stated, 70 per cent of the cases with satisfactory collapse have completely cleared their effusions following the use of merthiolate, and 30 per cent have definitely improved, so far as the effusions are concerned. No case is classed as unimproved, as was not true in the aspira-

TABLE 2

TREATMENT	NUMBER OF CASES	TYPE OF FLUID	DEGREE OF COLLAPSE	NUMBER MAINTAINING COLLAPSE	NUMBER ALLOWED TO REEXPAND	OLEOTHORAX	THORACOPLASTY	TOTAL DEATHS FOLLOWING ALL TYPES OF TREATMENT
Routine	155	Serous	Satisfactory, 104 (67%)	83 (80.0)	10 (9.6)	2 (1.8)	0	9 (8.6)
			Unsatisfactory, 51 (33%)	7 (13.7)	10 (19.6) 4 dead	1 (1.9)	5 (10.0)	36 (70.5)
		Grand total	Satisfactory and unsatisfactory, 155 (100%)	90 (58.0)	20 (13.0) 4 dead	3 (2.0)	5 (3.2) 3 dead	45 (29.0)
Aspiration alone	38	Serous	Satisfactory, 27	18 (66.6)	6 (22.3)	2 (7.4)		1 (3.7)
			Unsatisfactory, 11	1 (9.1)	0	1 (9.1)	1 (9.1)	8 (72.7)
	37	Seropurulent	Satisfactory, 22	15 (68.2)	3 (13.6)	2 (9.1)		2 (9.1)
			Unsatisfactory, 15	4 (26.6)	2 (13.3)	3 (20.2)		6 (39.9)
	25	Purulent	Satisfactory, 6	3 (30.0)	0	2 (33.3)	0	1 (16.7)
			Unsatisfactory, 19	4 (21.0)	4 (21.0)	4 (21.0)	2 (10.6) 1 dead	6 (31.6)
	100	Total	Satisfactory, 55	36 (65.5)	9 (16.4)	6 (10.9)	0	4 (7.2)
			Unsatisfactory, 45	9 (20.0)	6 (13.3)	8 (17.7)	3 (6.7) 1 dead	20 (44.4)
	100	Total	Satisfactory and unsatisfactory, 100	45 (45.0)	15 (15.0)	14 (14.0)	3 (3.0)	24 (24.0)
Aspiration plus dyes	2	Seropurulent	Satisfactory, 0					0
			Unsatisfactory, 2					2 (100.0)
	33	Purulent	Satisfactory, 13	5 (38.6)	3 (23.0)	3 (23.0)	1 (7.7)	1 (7.7)
			Unsatisfactory, 20	2 (10.0	4 (20.0)	2 (10.0) 1 dead	1 (5.0)	12 (60.0)
	35	Total	Satisfactory, 13	5 (38.6)	3 (23.0)	3 (23.0)	1 (7.7)	1 (7.7)
			Unsatisfactory, 22	2 (9.9)	4 (19.8)	2 (9.9)	1 (4.9)	14 (63.6)
	35	Total	Satisfactory and unsatisfactory, 35	7 (20.0)	7 (20.0)	5 (14.3)	2 (5.7)	15 (42.8)

Merthiolate irrigations	1	Serous	Satisfactory, 1 Unsatisfactory, 0	1 (100.0) 0				
	8	Seropurulent	Satisfactory, 7 Unsatisfactory, 1	7 (100.0) 0	0 1			
	19	Purulent	Satisfactory, 15 Unsatisfactory, 4	12 (80.0) 1 (25.0)		2 (13.3) 0		1 (6.7) 3 (75.0)
	28	Total	Satisfactory, 23 Unsatisfactory, 5	20 (87.0) 1 (20.0)	0 1 (20.0)	2 (8.7) 0		1 (4.3) 3 (60.0)
	28	Total	Satisfactory and unsatisfactory, 28	21 (75.0)	1 (3.6)	2 (7.2)		4 (14.2)
All mechanically treated cases	91 72	Grand total	Satisfactory, 91 Unsatisfactory, 72	61 (67.0) 12 (16.6)	12 (13.2) 11 (15.3)	11 (12.2) 10 (14.0)	1 (1.0) 4 (5.7)	6 (6.6) 37 (51.4)
	163	Grand total	Satisfactory and unsatisfactory, 163 (100%)	73 (44.8)	23 (14.1)	21 (13.0)	5 (3.0)	43 (26.4)

tion and dye groups. For this reason we have substituted merthiolate irrigations for routine aspiration and the use of dyes in the treatment of tuberculous empyema. Even in the unsatisfactorily collapsed cases, we believe that merthiolate irrigations will prepare the patient for thoracoplasty in a much more satisfactory manner than routine aspiration of the pus or treatment with various dyes.

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THE USE OF GRAPHIC RECORDS IN ARTIFICIAL PNEUMOTHORAX[1,2]

BURGESS GORDON

Collapse of a tuberculous lung by means of artificial pneumothorax has become a universally accepted procedure (1). In properly selected cases the toxic effects of the disease are controlled, the spread of infection in the diseased lung and to the opposite and hitherto unaffected lung is prevented, and healing is apparently accelerated; of great importance is the fact that prolonged rest in bed is unnecessary. Unfortunately, as with other procedures, the dangers and limitations are not always appreciated until a serious accident occurs.

Two types of reactions have been noted in artificial-pneumothorax treatments: One is immediate, due in most instances to improper technique; the other is delayed and usually related to influences operating more or less independently of any single treatment. The former manifest themselves by thoracic pain, weakness, shock, or some pulmonary symptom. The serious features are injury of the lung causing haemoptysis or air-embolism; rupture of a pleural adhesion, causing a spontaneous pneumothorax; penetration of the diaphragm, especially in phrenic-paralysis cases, with damage to the abdominal organs; trauma of the chest-wall, resulting in a subcutaneous emphysema; and rarely a reflex phenomenon, so-called pleural shock. The delayed reactions are characterized by the extension of disease to the contralateral lung, because of extra work thrown upon it, or by a disturbance of the pulmonary circulation due to displacement of the heart and mediastinum, which is often traceable to high intrapleural pressures.

Although incorrect methods are often responsible for the immediate reactions, the exact causes are sometimes difficult to establish. This is especially true when the technical details are carried out routinely. Evidently there is always the possibility of slight errors in recording the manometric readings.

[1] From the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, Pennsylvania, and the White Haven Sanatorium, White Haven, Pennsylvania.

[2] Reprinted, with additions, from *Medical Papers*, dedicated to Dr. Henry A. Christian, The Waverly Press, 1936.

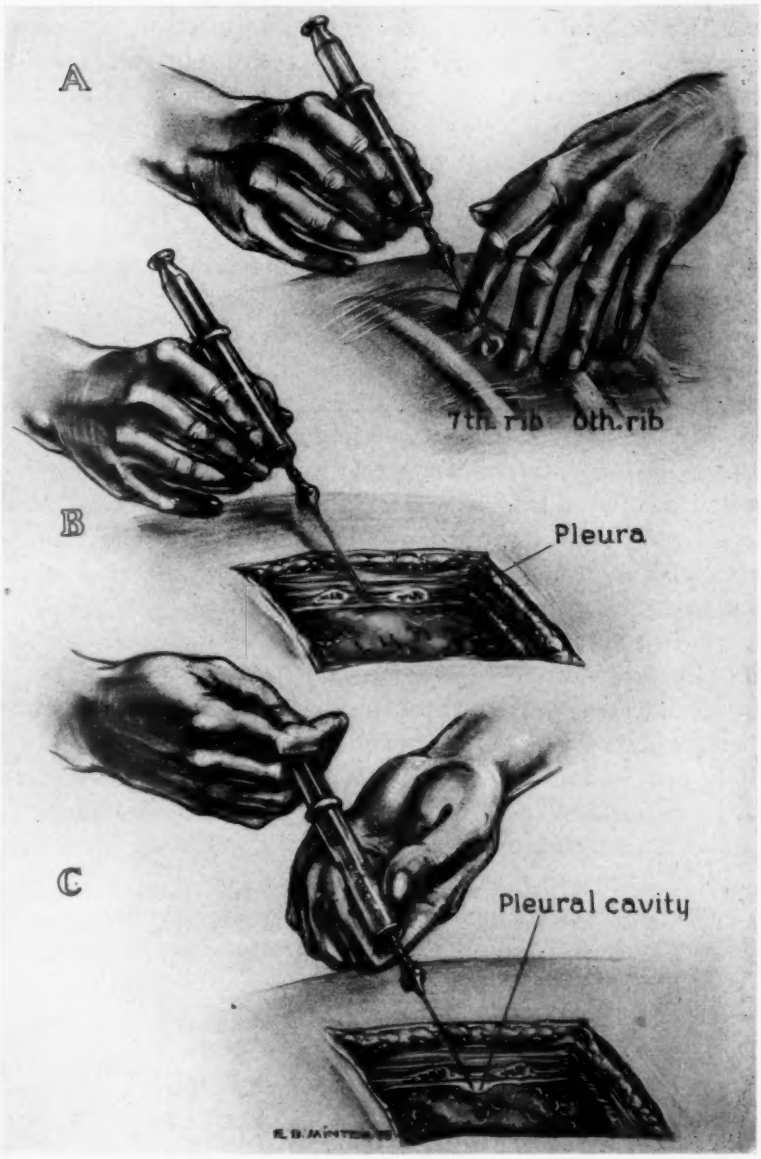
It has been found in the study of artificial-pneumothorax reactions that the records are not always sufficiently accurate or complete for critical analysis: as, for example, in the usual practice, only the highest and lowest degrees of intrapleural pressures are noted at the beginning and at the end of the treatments. Obviously a full tabulation of the interval variations would be difficult, and yet one may appreciate the value of a complete record in case of a serious development. An illustration is the change in the types of excursions of the manometric column as the pneumothorax needle is moved momentarily from the pleural space into the lung; another example is the sudden variation, often transient, that occurs with the sudden enlargement of the pleural space due to stretching of an adhesion.

In order to throw light on the nature of the complications in artificial pneumothorax a recording type of artificial-pneumothorax apparatus was devised (2). The important features are the recorder consisting of an aneroid and concentric assembly, which record the intrapleural pressure, the kymograph and a needle-valve for finely regulating the flow of air; the recorder corresponds with the manometer employed in the usual type of apparatus. The instrument was used at first experimentally in animals and later in more than 500 patients.[3] The tracings were studied during the introductions of air and following a series of treatments, with special reference to phenomena that would indicate the unsafe or incorrect positions of the needle in the thorax. The typical graphs and their significance are shown in the accompanying illustrations.

In figure A the technique for anaesthetizing the skin and deeper tissues is shown. In figure B the artist has cut a window to illustrate the position of the needle at the parietal pleura. Figure C shows the needle in the pleural cavity and the displacement of the visceral pleura; with removal of the syringe a small amount of air enters the pleural cavity by reason of the negative intrapleural pressure, which creates a localized collapse of the lung. The position of the needle in the pleural cavity is definitely established by reconnecting the syringe and withdrawing the plunger. With this, bubbles rise in the column of fluid. The needle has been introduced at the slight angle of about 85°. With this technique the tip of the needle displaces the visceral pleura as it is "slipped" into the pleural cavity. Thus, there is apparently less danger of penetrating the visceral pleura than with the usual perpendicular introduction.[4] The

[3] The instrument is manufactured by the George P. Pilling & Son Company, Philadelphia.

[4] The technique for introducing the pneumothorax needle was studied with the assistance of Dr. C. W. Semish.

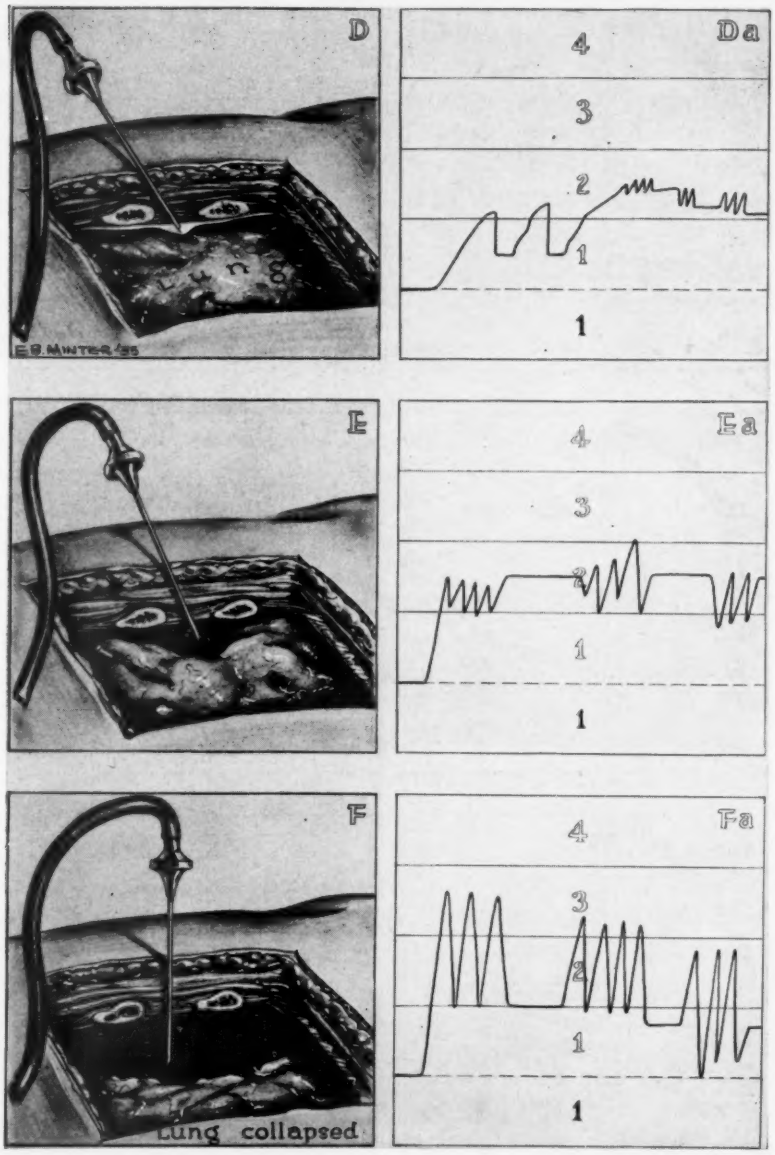


Figs. A, B & C. The technique of anaesthesia and the introduction of the needle in an initial artificial pneumothorax

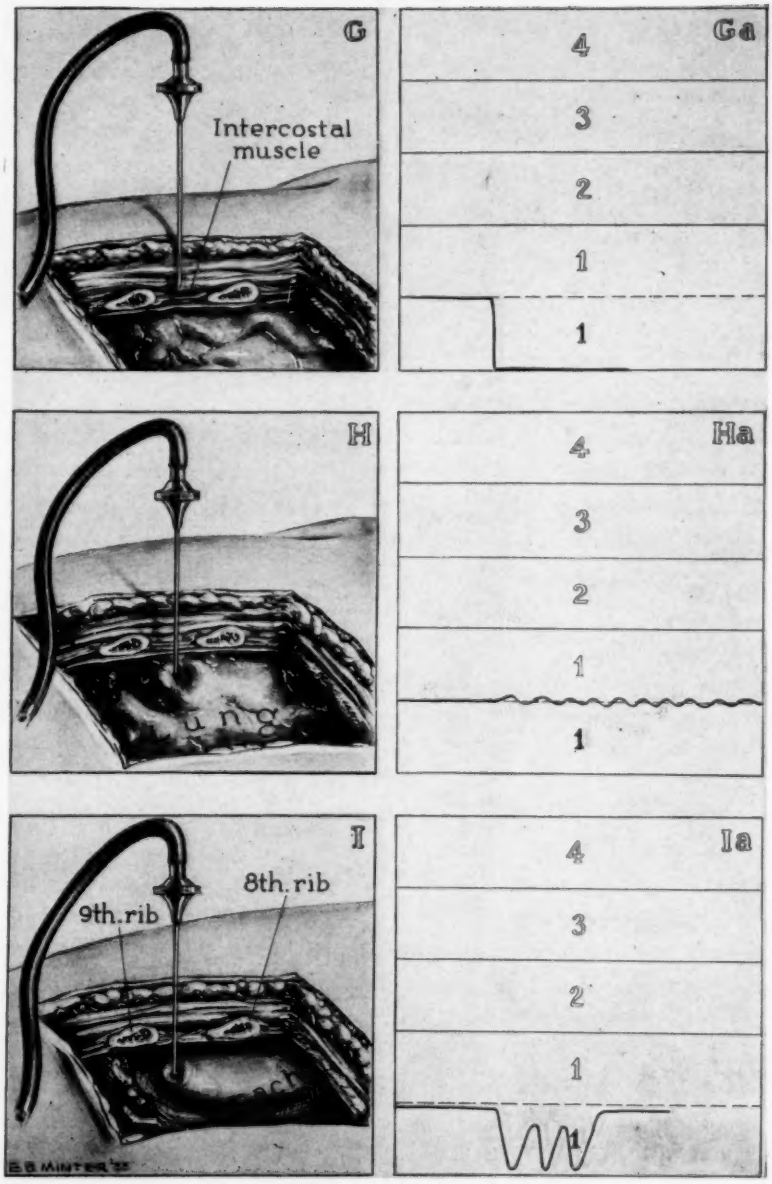
charts in the accompanying figure D and in the succeeding illustrations show spaces designated 1, 2, 3 and 4 in light numerals and a single space designated by a heavy numeral 1. The series of four spaces above the broken line, or neutral line, represent the negative zones; the space below the broken line is the positive zone; each space is equivalent to 2 cm. of water in a water manometer. The tracings in figures Da, Ea and Fa have been reproduced from graphs obtained from patients; the remaining graphs which illustrate faulty technique were obtained from animals.

Figure D illustrates a case of initial pneumothorax, the needle being connected with the recorder by means of a rubber tubing. The recorder was kept "open" during the first stage of the operation. The accompanying chart (Da) shows a gradual rise of negative pressure, due to separation of the pleural surfaces. A small amount of air was introduced on two occasions, as noted in the sharp decline of the negative pressure (an approach to positive pressure); with each introduction of air (the short horizonal lines) there was a rise of the graph indicating an increase of negative pressure, the result of a further separation of the pleural surfaces. Subsequently, the graph terminates in a series of small oscillations showing that the pleural space has become enlarged and contains sufficient air to be affected by the excursions of the lung. At this stage of the procedure the recorder is "cut off" during each introduction of air, as indicated by the short horizontal lines. The effect of the introductions is shown by the stair-like approach of the graph toward the positive zone, indicating a decrease in negative pressure. In figure E a further collapse of the lung is noted. The position of the needle is perpendicular, which is satisfactory and safe for this stage of the collapse. The tracing shows that with each introduction of air there is an increase in the depth of the oscillations and a gradual approach toward the positive zone—a decrease in the negative pressure. This phenomenon is illustrated more graphically in figure F, in which the lung is about 50 per cent collapsed.

Illustrations G, H and I show the effects of faulty technique in animals. In figure G the needle has entered the intercostal muscles, and, as would be expected, the aneroid failed to oscillate. Without a further attempt to enter the pleural cavity, about 5 cc. of air was released from the reservoir and the graph moved to the positive zone, but showed no oscillations. This abrupt increase of positive pressure without any movement which would correspond with the respiration shows that the air was introduced into a "pocket"; the graph is in marked contrast with the curves obtained



Figs. D, E & F. The collapse of the lung and the corresponding intrapleural pressures in progressive artificial pneumothorax

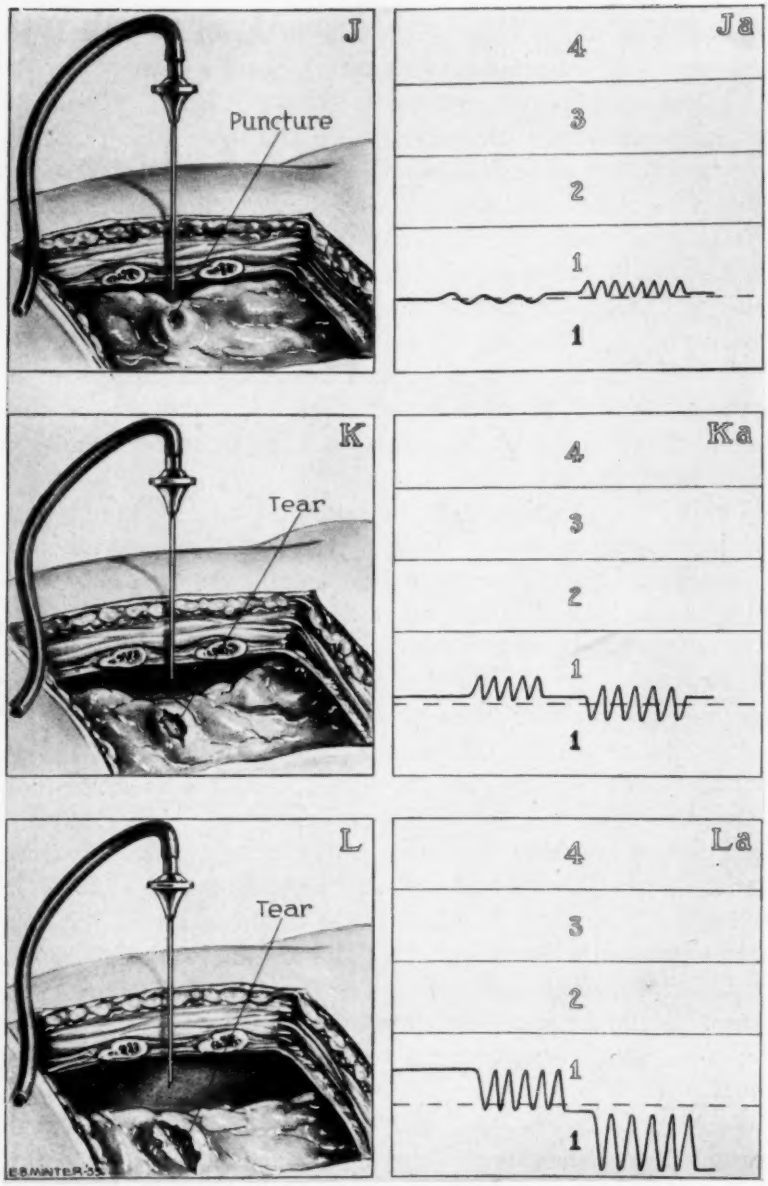


Figs. G, H & I. Examples of faulty technique with corresponding graphs in artificial pneumothorax

from the pleural cavity (Fa). In figure H the needle has entered the lung and the peculiar "wavy" graph is typical of the variations of intrapulmonary pressure. The failure to obtain any sustained rise of negative or positive pressure indicates that the needle is not in the pleural cavity. With the introduction of air under such circumstances there would be a strong possibility of air-embolism. Illustration H emphasizes the danger of penetrating the visceral pleura in the initial cases of artificial pneumothorax when the needle is introduced perpendicularly. Illustration I shows the needle plunged into the stomach, a situation which is not difficult to imagine in cases with elevation of the diaphragm due to phrenic paralysis. The accompanying graph (Ia) shows positive excursions with curved peaks, which are somewhat characteristic of the variations of gastric pressure as influenced by movements of the diaphragm. Except for these curious peaks the tracing resembles those obtained from the pleural cavity (figure F).

It is noted in illustrations J, K and L that the lung has been punctured by the pneumothorax needle. In figure J the needle entered the lung and was subsequently withdrawn into the pleural cavity. This caused an opening in the lung with the result that air escaped into the pleural space, thus creating a spontaneous pneumothorax. The "wavy" oscillations in the graph (Ja), as noted previously (Ha), show the variations of intrapulmonary pressure while the needle remains in the lung. The horizontal line connecting the series of oscillations represents a period of 5 minutes while the aneroid was shut off and the needle was withdrawn into the pleural cavity. During this period air passed from the lung into the pleural space. After the development of a spontaneous pneumothorax the typical intrapleural oscillations were obtained, as shown in the second series of curves. In figure K the escape of air into the pleural cavity has gradually increased, and the accompanying graph (Ka) shows the reduction of negative pressure and later the development of a positive pressure. A similar situation is illustrated in figure L, except that the passage of air has been more rapid, causing a marked increase of positive pressure.

Undoubtedly, numerous advances have been made in clinical medicine because of the availability of graphic records. Witness the rôle of the electrocardiogram in the study of cardiac disorders and the graphs obtained in basal metabolism. Without these it would be difficult to explain certain mechanisms or carefully follow and correlate the effects of treatment. The graphic record is also a check of technical efficiency,



Figs. J, K & L. The puncture of the lung and the corresponding graphs in faulty artificial pneumothorax.

which is especially valuable when the studies or treatments are carried out by different workers. The present study suggests that tracings are practical as well as critical in the routine treatment of tuberculosis by means of artificial pneumothorax. They are of special value in studying unexplained reactions.

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A NEW ARTIFICIAL-PNEUMOTHORAX APPARATUS

SIDNEY HIRSCH[1]

The salutary effect of collapse therapy on pulmonary disease has been amply demonstrated. Artificial pneumothorax has proved itself the simplest means of collapse therapy. It has become a standard method of treatment. Its popularity would be much greater if the present varieties of the apparatus for its production were not so cumbersome and if it were simpler to manage. Since 1904, when Saugman introduced the water manometer, this type of apparatus, elaborated in many ways, has been the most popular, but its technical difficulties have greatly reduced the application of this valuable procedure. To eliminate these objections, I have devised an apparatus which can be carried in an ordinary bag, which is more compact, more easily managed and quite as accurate as the water instrument. It is easily controlled and is always ready for use. It admits easy insufflation of measured air and at the same time permits an accurate reading of positive or negative intrathoracic pressure. It is a practical, "fool-proof," portable machine for instant use anywhere. The aneroid gauge supplanting the water manometer eliminates the worry over the spilling of fluid in the leveling bottles or its freezing in cold weather. The readings are obtained without calculation. It performs with facility all functions demanded of any pneumothorax apparatus:—exact initial fillings with filtered air; correct measured refills; creation of high intrapleural pressure when indicated; easy adaptability for *thoracentesis*, as in pleural effusion, or in the removal of air, as in spontaneous tense pneumothorax. The readings are also more rapid than with the water manometer because the indicator needle responds instantly to changes in pressure whereas the fluid in the water manometer has a variable lag or inertia.

The apparatus illustrated consists of a simple automatic 2-way valve (figure 1) and air-gauge. The valve permits the use of a small (10 cc.) syringe as a pump to transmit a measured amount of air to the patient.

[1] Senior Surgical Clinical Assistant, Mount Sinai Hospital, New York.

Directions for use: Before insufflation, the stopcock is turned to the air-gauge, to determine when the point of the needle is in the pleural cavity. This is demonstrated by the excursions of the gauge whose *maximum* reading equals 40 cm. of water-pressure, either positive or negative. It responds with great sensitivity to all pressure fluctuations.

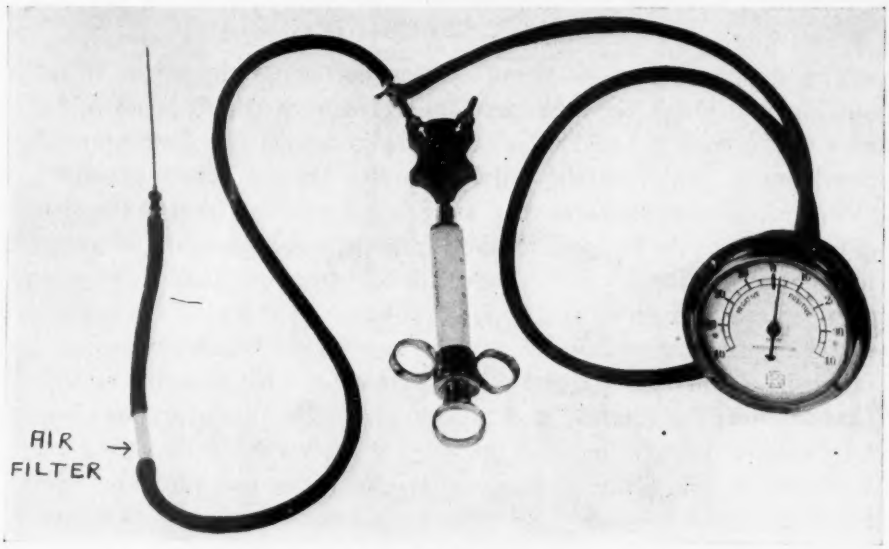

Fig. 1

A small quantity of air, approximately 25 cc., is pumped into the pleural cavity. If the gauge still shows a negative pressure, the gradual introduction of air may be continued until 200 to 250 cc. have been introduced, producing the desired reading of the intrathoracic tension. The adaptation of the aneroid barometer to replace bottles, flasks or jars followed the suggestion of Dr. Howard Lilienthal when the suction-transfusion automatic valve was demonstrated to him. Dr. Lilienthal has since given his unqualified approval to the completed apparatus. I am grateful for his interest and coöperation.

I also wish to express my thanks to Dr. J. Burns Amberson, Jr., Dr. Coleman B. Rabin and Dr. Arthur S. W. Touroff for their application of my apparatus to clinical tests.

AN HOUR-GLASS ARTIFICIAL-PNEUMOTHORAX APPARATUS[1]

MILTON SILLS LLOYD

The apparatus consists of two 200-cc. bottles, graduated in 50 cc., one inverted above the other and connected by a double-faced rubber cork. The cork is fitted with a specially constructed valve (figure 1), providing an outlet to the bottles through three separate apertures. One of these communicates with an air vent reaching from the bottom of one bottle to the bottom of the other, and can be reversed in direction by rotating the inner valve cylinder one half-turn, or closed by rotating it one quarter turn from the working position. The second is a straight liquid transfer channel, which may be closed by a quarter-turn, but is otherwise open. The third also communicates with a simple straight channel, but, like the first, it may be reversed by a half-turn, or closed by a quarter-turn. The three openings are so arranged that their vertical portions lie in the same plane, and apertures one and three communicate between opposite bottles and the outside air. It is evident therefore that a quarter-turn from the working position closes all three, while a half-turn causes apertures one and three to communicate with alternately opposite bottles. (See figure 1.) The air outlet (O) and the air inlet (I) may be connected by tubing to one branch of a "T" style three-way stopcock, the other two branches of which connect with a "U" water manometer, 25 cm. high, and a tube which leads to the chest. A suitable adjustment of this stopcock will place any two or all three of its branches and the rubber tubing connected thereto in a closed system.

To use the apparatus, the valve on the hour-glass air-supply mechanism is set at the "off" position. The bottles are then placed so that the one containing the liquid is uppermost. A manometer reading is obtained in the usual way. The valve is placed in the position indicated in figure 1. The liquid immediately begins to flow from the upper to the lower bottle. As the upper bottle is emptied, air is drawn in through the inlet aperture by way of the air vent, and as the lower bottle is filled, air is displaced through the outlet aperture to the chest.

[1] Read at a meeting of the New York Society for Thoracic Surgery, November 27, 1936.

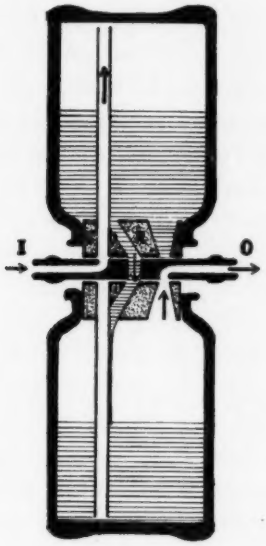

Fig. 1

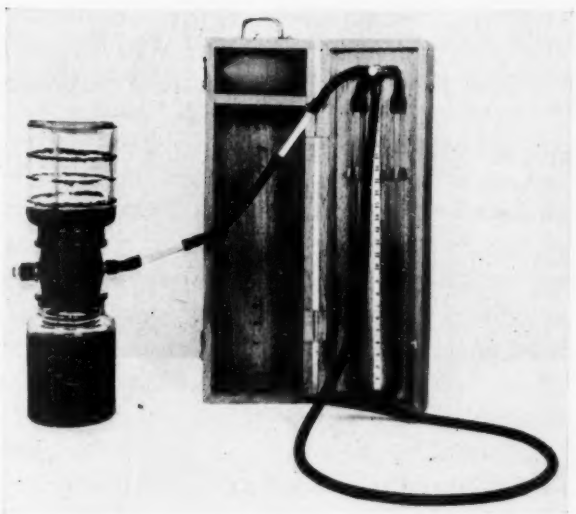

Fig. 2

The usual cotton filter is inserted between the bottles and the manometer.

The rate of flow may be regulated by placing the valve either full "on" or only partially "on." When the upper bottle is empty, the valve is

turned "off"; the bottles are inverted, and the process is repeated. In order to deflate with the same degree of control in respect to pressure and volume of air, it is only necessary to change the connecting tube to the "inlet" end (I) of the air-control valve. Air is delivered to or drawn from the chest at a pressure which varies from 14 to 3 cm. of water above or below atmospheric, depending upon the distance between the surface levels of the liquid in the two bottles and the end of the air-control valve to which the tubing is connected. If the administration of air under high positive pressure is desired, a positive-pressure air pump is attached to the inlet end of the valve, and the liquid is forced from the upper to the lower bottle until the desired pressure is reached. If a high degree of negative pressure is desired, a negative-pressure air pump is attached to the outlet end of the valve and the liquid evacuated from the upper bottle until the desired degree of negative pressure is reached. In ordinary usage, the assistance of these pumps is not necessary.

The complete apparatus is contained in a wooden case, with a compartment above the bottles to provide space for needles, connecting tubes, etc. It weighs less than three pounds, can be carried in the ordinary physician's bag, and yet answers to every requirement which can be made upon a pneumothorax instrument. The air-control valve is made of noncorrosive metal, so that plain water may be used in the bottles.[2]

The apparatus ready for use is shown in figure 2.

[2] This apparatus is made by the George P. Pilling & Son Co., Philadelphia.

THE SURGERY OF THE TUBERCULOUS BELONGS TO THE SANATORIUM[1]

E. L. ROSS[2]

The spectacular irruption of Science into Medicine in the past half-century changed, and has constantly kept changing, all our concepts about tuberculosis. Indeed, the bacillus of Koch, the ray of Roentgen and the techniques of the new surgery have created an entirely new epidemiology, a new living pathology, a new diagnosis, and a new treatment. It is a far cry from Trudeau and his "Little Red" to even the minimum routine of the most remote and isolated sanatorium of to-day. Every year the routine becomes more elaborate. Every year more can be done for the care of the individual and for the clearing up of disease in the community.

It may be of interest to survey what the day's work has become in a comparatively isolated Sanatorium. The Manitoba Sanatorium, which I will naturally take as a specimen, is about 150 miles from the chief medical centre of the province. It began a little over a quarter of a century ago with the least that could possibly be done with in equipment, depending upon outside help for almost everything but the rest-diet routine, and now finds that it should itself undertake just about all that the patients need either in the new ways of diagnosis and treatment or in emergencies.

It is generally considered to-day that an institution treating pulmonary tuberculosis is not up-to-date unless some form of collapse therapy is considered for every patient, and indeed unless a majority of resident patients have collapse in some form employed. The indications and shortcomings of pneumothorax are constantly becoming better understood; phrenic-nerve surgery is on a firmer basis than even five years ago, and pneumolysis is now an essential adjunct to pneumothorax. Thoracoplasty, with its improved techniques, is becoming less formidable, and its application early rather than late justifies its consideration not for rare, bad cases only, but for all not doing well, or not likely to go on steadily to full recovery, on other treatment.

[1] Read at a meeting of the Canadian Tuberculosis Association at Vancouver, June, 1936.

[2] Manitoba Sanatorium, Ninette, Manitoba.

At the Manitoba Sanatorium for 22 years we have been staunch believers in collapse therapy. On December 31st, 1935, of a total of 265 patients, 241, or 81 per cent, were primarily on treatment for pulmonary tuberculosis. Of the 241, 197, or 82 per cent, were having or had had some form of lung collapse therapy. With such a high proportion, we sometimes raise the question as to whether we are not too radical and too impatient. However, the day of shelving and hoping is past. The mortality from tuberculosis is still high, and with such a killing disease the more drastic measures in treatment must be considered and their risks must be taken. The very bold treatment of yesterday is the standard good treatment of to-day.

Of the 241 mentioned above, 119, or nearly 50 per cent, are at this time having pneumothorax treatment (12 of these bilateral). In recent years appraisals of the results of pneumothorax treatment generally have been rather disappointing. The dramatic successes are remembered, but, unless records are closely surveyed, the failures are soon forgotten. These failures do not belittle the principle of lung-collapse therapy, but usually call in question the stage at which it is begun or its long continuance with partial or unsatisfactory improvement. The results can be improved and the complications lessened by applying it to smaller lesions and at earlier stages, by improving the collapse through the severing of pleural adhesions, and by stopping early a pneumothorax if it is not collapsing the cavity or the diseased portion of the lung. Continuing such discouraging pneumothoraces, we not only fail in our objectives but court complications.

Pneumolysis has been resorted to in 39, or over 30 per cent, of the 119 active pneumothorax cases. Even if the facilities, and the experience of the medical staff are such that major surgery cannot be done, the place for closed pneumolysis without doubt is wherever pneumothorax is given and that is wherever tuberculosis is treated. With his intimate knowledge of the ups and downs the patient has had, having followed him by symptoms, film and fluoroscope, and with his greater experience in the interpreting of chest films, the sanatorium physician is the logical person to deal with the complicating adhesions. Special surgical experience and skill help, needless to say, but a sanatorium doctor of ordinary skill and experience, who is interested, deft and patient, can manage the intricacies of this procedure. Knowledge as to selection of suitable cases and judgment about what should and should not be cut develop by experience. In this, as in all measures for sanatorium patients, clinical experience and insight are the great bases for decisions.

The early enthusiasm for surgery of the phrenic nerve has subsided, and this procedure seems to be settling down to a more logical place in treatment. It can be a really useful measure, especially the crushing operation, and, combined with pneumothorax or pneumolysis, may give sufficient relaxation to allow an effective collapse. Twenty-one per cent of our patients with pulmonary disease have had a phrenic crushing or evulsion. Several of these procedures were combined with the earlier thoracoplasties, but for the past few years this operation is not done, certainly not an evulsion, as a preliminary to thoracoplasty.

Thoracoplasty is evolving through the same stages as pneumothorax. If applied in cases otherwise hopeless, there cannot but be failures. In appraising thoracoplasty, what is more important than counting up the postoperation deaths is the counting up of cures. If the objective is the best possible statistical showing, many will be denied a life-saving measure who should have had the added chance. As thoracoplasty has changed, the range of its patients has changed. It is considered very much earlier than it was. Evidence of fibrosis is an advantage, but, if waited for, may never come; and, even if it should come finally, the prolonged period with positive sputum, the prolonged toxaemia and invalidism and the resulting impaired function of vital organs, the lung by no means least, increase the operation risk and the danger of an unsatisfactory outcome. A few years ago a man was operated upon for conditions already present, and it was his past history that was canvassed. Now he is operated upon to prevent bad conditions from becoming worse. It is his future chances that are canvassed. The risk of not operating is more considered than the risk of operating. Diagnosis has dropped to second place and prognosis becomes the chief basis for decisions.

Unilateral disease offers a better outlook with thoracoplasty, quite naturally, as it does also with pneumothorax, or without either measure, but, if the disease is bilateral, major surgery is by no means contraindicated. In a series of 46 cases, operated on in a little over a year, 24, or 52 per cent, had moderately or far-advanced disease in the better lung. If the contralateral disease has been stationary for from four to six months, and if a cavity in the bad lung is productive of a considerable amount of positive sputum, the risk of not operating is greater than the risk of operation. Complicating laryngeal or intestinal tuberculosis, unless with troublesome symptoms, and considered to be the predominant feature, should not prohibit thoracoplasty. Actually, the

need for any measure that will improve the primary disease is the greater because of complications.

At the end of 1935, 47, or nearly 20 per cent, of the patients with pulmonary disease in the sanatorium have had thoracoplasty. During the past 13 months, 98 operations have been performed on 46 patients, with three deaths attributable to the operation, and in all three disease was of many years' duration. In those observed for six months after their last stage, 79 per cent have now sputum negative for bacilli, not only by ordinary sputum smear but also in gastric contents and cultures. Incidentally, this method of search for bacilli in gastric contents and also the culturing of sputum reveal many sputum-positive who by ordinary methods of examination were sputum-negative. It is also of interest to note that, of the 98 thoracoplasty operations, all but three were done entirely under local anaesthesia.

The past year corresponds almost exactly to the time during which we have been equipped to do thoracoplastic surgery. At the beginning and for many years, we considered that the function of a country sanatorium was wholly medical and that it should not need to provide skill even to remove a troublesome appendix. But now that surgical measures are so very essential, so generally needed, and so often used, the only right plan is to have them as fully and readily available to the patients where they are, and when they need them, as pneumothorax is. This is a view sanatorium men seem to have been spontaneously driven to in the past few years, for few now will let needed daily surgical service depend upon the occasional visits of consultants.

We were particularly fortunate in our consultants, beginning with Dr. W. L. Mann, who was the pioneer and still is the dean of chest surgery in Western Canada. He with Dr. B. H. Olson have been always ready to give us of the very best in sound judgment and wise teaching. What we may have learned, and what judgment we may have formed, we owe very largely to them, and we hope to increase this indebtedness in the years to come. But we have been driven to the conclusion that patient and surgeon should not be 150 miles away from each other, partly because the surgeon cannot come to the patient often enough or regularly enough (and it may be not at all in winter), and partly because the patient loses altogether too much that is vital to him when he goes 150 miles to the surgeon.

One hundred and fifty miles' travel by any way of transportation cannot possibly be other than a handicap and a disadvantage to a sick man,

tiring, disturbing and energy-consuming, with always the danger of picking up extraneous infections. For every sick man considered for thoracoplasty there is an optimum time, even almost an optimum day for the operation. For this most favorable time, symptoms and temperature, blood pictures, chest films and gastrointestinal phases are considered day by day. When the day comes, this more favorable phase must not be spent and lost on a railway journey nor on the upsets of changes in environment, changes in hospitals, and in medical and nursing care. There are accustomed ways, personal tendencies and idiosyncrasies that strangers cannot know. The postoperation nursing of the tuberculous man demands knowledge of the man himself, of tuberculosis nursing in general, and certainly of chest surgery in particular, a knowledge much more likely to be found accumulating in the more permanent nursing staff of a sanatorium than in the changing staff of the school-hospital he may be sent to.

Close, understanding medical care, as well as nursing care, is especially important after a chest operation. A general surgeon can seldom give time to see to all details. For a sanatorium physician-surgeon who is resident this is his chief work. He has ample time to do dressings and supervise general care personally and meticulously. Ways for position after operation have to be devised anew for each patient, for getting rid of expectoration, and quantity and kind must be closely watched. Proper exercising of the arm and shoulder and the applying and adjusting of compression appliances are all important matters that need the utmost care. The sanatorium physician, with his daily experience in tuberculosis and with special training in chest surgery in addition, is better fitted for this work than a general surgeon of possibly greater skill but without an intimate clinical knowledge of tuberculosis. There is probably no branch of surgery that needs closer team-work in medical and nursing care than chest surgery.

The work and study of physician, surgeon, radiologist, and laboratory worker all need to be closely correlated, as all can be at a sanatorium. The technique of taking chest films is usually developed more closely there also. Post- and preoperation films can be worked through with more thought and study and with a more accurate comparative technique by sanatorium surgeon and X-ray technician than by those who do not devote their whole time to this kind of work. We often consider we need both posteroanterior and anteroposterior exposures, sometimes dense or semi-dense films, and almost always special films of the apices. (Inci-

dentally, for sixteen years X-ray studies of the intestinal tract by barium meals have been made as a routine. In this way changes are found early and treatment altered or intensified appropriately.) Various pre- and postoperation laboratory examinations are necessary, and, as with the X-ray, a sounder interpretation of such tests in relation to tuberculosis should be expected in a sanatorium, as they comprise most of the regular daily work. No sanatorium can get along to-day without a well-equipped and enthusiastic laboratory service. It should have in use all the super-methods for finding tubercle bacilli in sputum, urine, spinal fluid, pleural fluid, stomach contents or faeces. Differential blood counts and the sedimentation estimation should be done as a routine and are becoming more important yearly in determining prognosis, and therefore in guiding treatment.

The time has come when the isolated sanatorium should have its bronchoscope and its cystoscope. It may not hope to have a specialist's knowledge and skill, but it should have some useful knowledge and skill. In short, the X-ray department, the laboratory, the operating room, the medical services and the nursing services should be equipped for almost anything that can be needed in diagnosis, prognosis or treatment. A sanatorium, which is a specialist institution for the care of the tuberculous, should be a specialist in every part of that care.

Surgery in a sanatorium adds to the work and worries of the medical staff and immensely also to nursing work and personnel. Indeed, from laundry, sewing-room, and power-house, throughout nursing and medical services, all departments are affected by the new responsibility. However, the interest in the day's work is greatly increased; there is a new satisfaction in the readiness to give more complete care, and patients have much greater confidence in what is done and can be done for them. After even just a year of being pretty much self-contained in surgery we have no regrets, and are more and more impressed by the advantages to the patient of his being able to get all his treatment under one roof. The surgery of the tuberculous, the bronchoscope, the cystoscope, the fullest laboratory and X-ray procedures do most good to the patient when they are readily and instantly available to the patient *just where he is.*

THE NECESSITY OF THE BRONCHOSCOPE IN MODERN CHEST WORK[1]

MAURICE G. BUCKLES

Bronchoscopy has long been presented as a separate and distinct specialty which may be applied to certain conditions of the lungs. Regardless of the excellent work by numerous men, it is still thought of by many in the light of foreign-body removal, and little attention has been given it concerning organic changes of the lungs and bronchi. It is my impression that the majority of sanatoria and chest clinics are not getting the maximum from the bronchoscope.

It seems to follow that the bronchoscopist should know thoroughly diseases of the chest and that the chest man should be able to think clearly in terms of the bronchoscope. It should occupy the same position as any other clinical aid for arriving at accurate clinical deductions, substituting for none of them, replacing none, but as a definite adjunct which gives to us the only method of observing the living pathological physiology and associated mechanisms of the tracheobronchial tree (Jackson (1)).

The procedure is not only indispensable in its present form from therapeutic and diagnostic viewpoints, but there is perhaps a vast store of knowledge yet to be gleaned by repeated study and observation of the bronchi in certain diseases. It is with the above in mind that I feel that a closer relationship between the subjects of diseases of the chest and bronchoscopy should be effected.

At Waverley Hills Sanatorium, the municipal sanatorium of Louisville and Jefferson County, we have for the past several months been doing our own endoscopic work (nearly one thousand bronchoscopies and laryngoscopies), and are enthusiastic concerning results from both therapeutic and diagnostic aspects. Special training is available and those already having a thorough working knowledge of the chest and associated with chest work will be pleasantly surprised at the clinical success of establishing a unit.

[1] Presented at a session of the Clinical Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, April 23, 1936.

We all see atypical X-ray films which do not conform to the usual pattern of tuberculosis, or any other known category. These cases may

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The X-ray films, Figs. 1 to 12, represent a number of cases in which we have proved the diagnosis by bronchoscopy:

Fig. 1. Pulmonary abscess, right cardiohepatic angle.

Fig. 2. Shows complete disappearance of abscess shadow one week after aspiration.

Fig. 3. Reveals shadow simulating atelectasis in the right base which was proved to be carcinoma. (Fig. A.)

Fig. 4. Female; age 36. Right pneumothorax. Has persistent streaking. Bronchoscopy reveals granulations with ulceration of the right lower lobe. (Fig. B.) 50 per cent silver nitrate was applied with no recurrence.

Fig. 5. Shadows in the right base were proved to be produced by adenocarcinoma of the right lower lobe. (Fig. C.)

Fig. 6. Patient gave history of recent haemoptysis. Due to displacement of the mediastinum and elevation of the diaphragm on the same side, atelectasis was investigated which showed obstruction to the left upper lobe bronchus.

Fig. 7. Shows the same case following bronchoscopy.

Fig. 8. Patient had left pneumothorax, positive sputum and extensive disease in the opposite lung. A loud wheeze developed, accompanied by progressive dyspnoea, over a month's time, to cyanosis. Due to physical findings and flattening of the right diaphragm with limitation in excursion, a diagnosis of obstructive emphysema was made. On examination, a benign adenoma was found to produce valve-like action of the right common bronchus, allowing a small amount of air to enter and very little to escape. (Fig. D.)

Fig. 9. Bronchoscopic investigation, followed by lipiodol filling, shows dilatation of the right middle and lower lobes. Multiple lobectomy was done.

Fig. 10. Male; age 45. Density in the right base. On bronchoscopic examination, squamous-cell carcinoma was found, producing atelectasis of the lower lobe.

Fig. 11. Apical radiopacity was proved to be papillary carcinoma. (Fig. E.)

Fig. 12. Female; age 45. Had complete thoracoplasty two years previously for control of haemorrhage in bronchiectasis. Has had streaked sputum since that time. Bronchoscopic examination reveals two ulcers on the right common bronchus. (Fig. F.) 50 per cent silver nitrate was used to cauterize these areas. No recurrence in streaking.

Figs. 13 & 14. Patient; age 36. Complained of cough and expectoration, with X-ray changes in the right apex and left base. Pneumothorax had been given this patient for tuberculosis. Investigation per bronchoscope with lipiodol revealed right apical and left basal bronchiectasis.

Fig. 15. Patient; age 35. Has had left pneumothorax a number of years with previous positive sputum. Cough and expectoration all out of proportion to the amount of disease shown on X-ray. Bronchoscopic examination reveals definite dilatation of the descending trunks. This was verified by lipiodol injection. Patient is kept comfortable by periodic aspirations.

Fig. 16. An unusual X-ray shadow. Male; age 55. Numerous diagnoses had been made over the past few months. Patient had no cough or expectoration. Bronchoscopic examination revealed no abnormalities. Saline lavage revealed a large number of tubercle bacilli.

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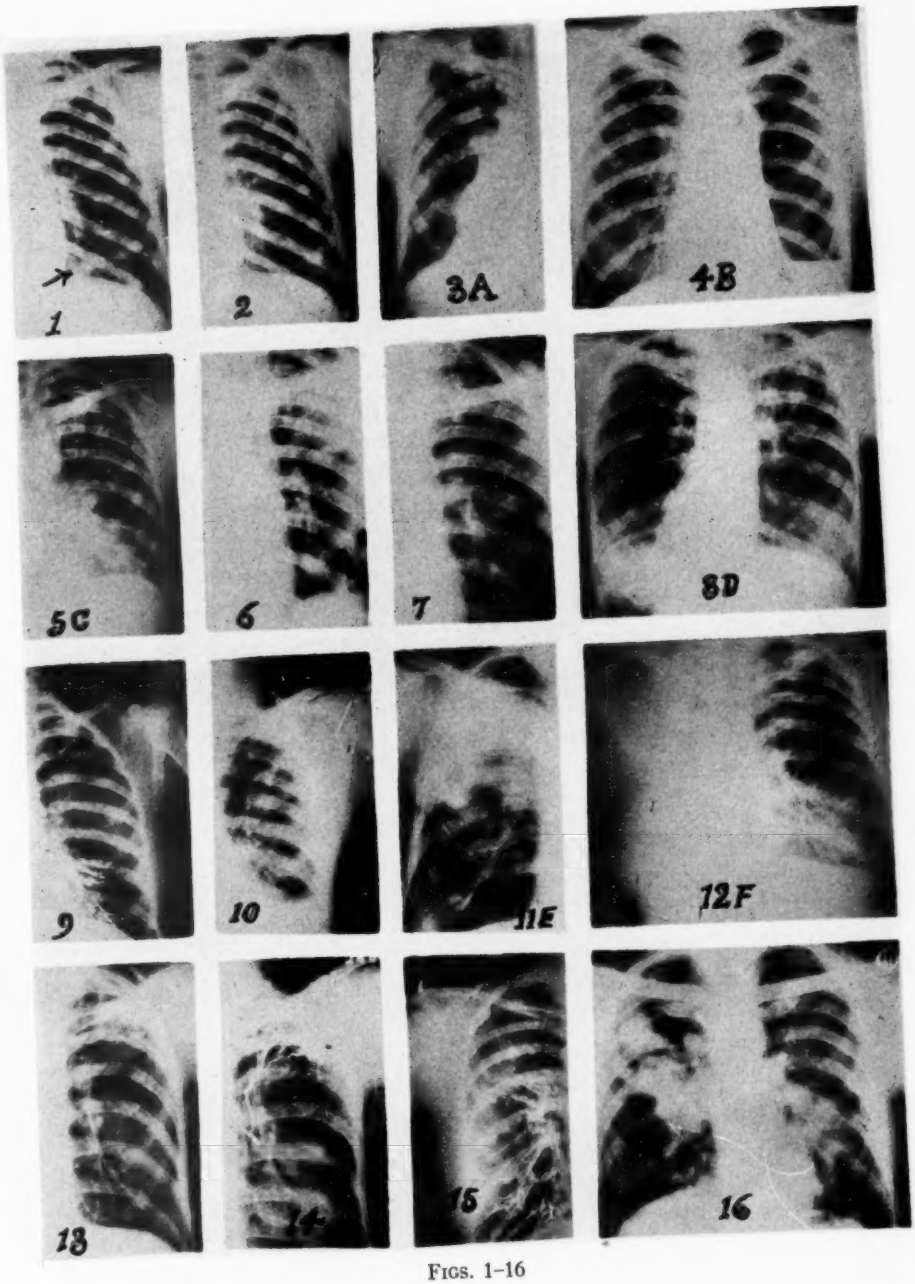
have symptoms compatible with many conditions so that the diagnosis is frequently one of speculation. In such cases we may not only add



FIGS. 1–16

much knowledge but also an accurate diagnosis and often therapeutic aid. In others the X-ray may not give a clue because larger bronchi and trachea may alone be involved. This is true in such conditions as early carcinomata of the bronchi, papillomata, ulcerations, atresias and granulations. With the tremendous number of bronchogenic carcinomata being reported (Clerf (2), C. L. Jackson (3), and many others, as well as our own smaller series, carcinoma being by far the most common pulmonary tumor according to Miller and Jones (4)), early diagnosis is all important if surgical removal is to be successful. Seventy-five per cent of primary carcinomata of the bronchi are discernible by the bronchoscope (C. L. Jackson and Konzelmann (5)).

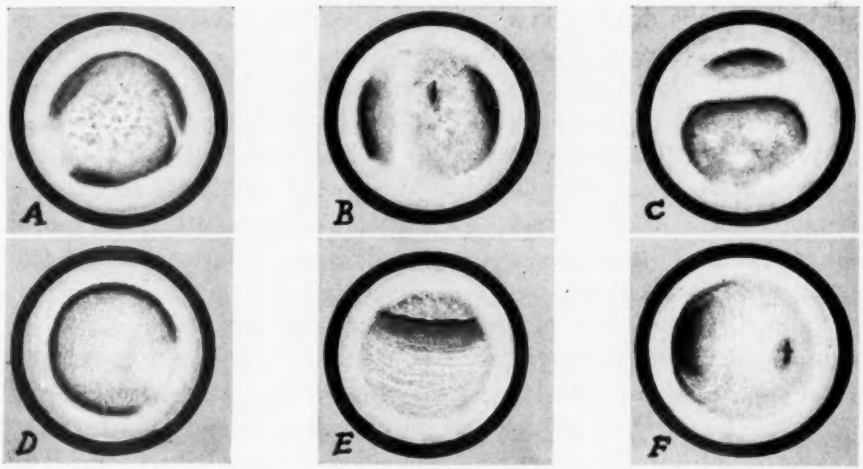
In tuberculosis work, when the diagnosis is already established, the indications are much more common than previously thought. Among the conditions which we have noted are polyps, ulcerations, granulations, stenosis of the bronchus and atresias. One case of posthaemorrhagic atelectasis was observed and immediately relieved by aspiration. Oedema of the uncollapsed lung was noted in one case of pneumothorax. Aspiration gave temporary relief, the patient dying at a later date when bronchoscopy was not available. In several cases we have had coexisting tuberculosis in one portion of the lung and bronchiectasis in another. Frequent aspirations may be necessary in such cases. Obtaining uncontaminated secretions for bacteriological study is not only important in tuberculosis but in all infectious processes. We have not thought repeated aspiration of the terminal cases of much value. Bleeding points in the bronchi have been found to explain recurrent haemoptysis and streaking in several cases. Careful study of the contour of the trachea and bronchi may give us a clue to lymph-node pathological processes in the mediastinum.

There are no contraindications to bronchoscopy in tuberculosis (Clerf (6)), even in the presence of pneumothorax or thoracoplasty, although there is no indication in the average case. We have done several in the presence of dyspnoea, cyanosis and extreme temperature (105°), when the indication was imminent from clinical study.

Bronchial obstruction demands interference, a persistent wheeze frequently being the earliest symptom. Thick, tenacious secretion may produce distressing symptoms, and may progress sufficiently to produce atelectasis with extreme dyspnoea. The Bechic blast and tussive squeeze (Jackson (7)) are both noted as being interfered with, following phrenic interruption. Haemoptysis has been known to be misleading as an indication to tuberculosis, and we feel that, when the clinical picture does

not clinch the diagnosis, bronchoscopy should not be deferred too long, as it may immediately give us the true pathological condition.

We prefer not to bronchoscope in the presence of active haemorrhage or immediately following it, unless indications of obstruction are present. In no case have we seen any evidence that harm was done to the tuberculous process.



Bronchoscopic Views

The above represent the gross views as seen through the bronchoscope on six of the previous X-ray films.

Fig. A. Squamous-cell carcinoma of the right descending bronchus, showing complete obstruction of the lower lobe and partial obstruction of the middle lobe.

Fig. B. Represents tuberculous granulations of the right common bronchus, with ulceration just below the bifurcation of the trachea on the medial wall. (Fig. 4.)

Fig. C. Adenocarcinoma of the right lower lobe producing atelectasis. (Fig. 5.)

Fig. D. A round smooth glistening adenoma of the right common bronchus producing obstructive emphysema. This benign tumor was removed with biopsy forceps and the stump cauterized with 50 per cent silver nitrate. No recurrence. (Fig. 8.)

Fig. E. Papillary carcinoma of the right common bronchus at the junction of the upper lobe. (Fig. 11.)

Fig. F. Ulceration on the lateral wall of the right descending bronchus. (Fig. 12.)

Note: All tumors proved by biopsy.

Bronchiectasis is becoming such a problem in chest clinics, due to its high incidence and morbidity, that it is demanding much attention. We consider most all cases as obstructive, and perhaps know something of the mechanisms producing the disease, though much is yet to be learned. The bronchoscope has and will throw much light on this problem. I feel that the proper approach is from a prophylactic viewpoint,

that is, properly recognizing the chronic cough, sinus pathological conditions, etc., alleviating, if possible, any basis for the formation of the disease. Prebronchiectatic phases should be borne in mind constantly. Early dilatation and aspiration of the bronchi may greatly facilitate emptying power, and at the same time removal of the obstruction may be affected.

Proper treatment and consideration of the cough so often following acute infectious diseases in children (Tucker (8)) cannot be overemphasized. This early thickened, inflamed, swollen bronchus of infancy, if neglected, may be the chief fundamental factor in the mechanism of bronchiectasis later in life. In the advanced cases, repeated aspiration may give much temporary relief. We feel as Ballon (9) does, that the progress of the disease may be checked in some cases. Relief of toxaemia is noticeable. Retardation of the secondary degenerative changes of other organs and lessening of the probabilities for recurrent bronchopneumonia should follow.

Pulmonary abscess, if obtained early, may be satisfactorily treated. Our experience leads us to believe that the time element is all important. Clerf (10) has shown that 70 per cent of early cases were cured. Bronchoscopy should not be carried past the optimum time for open drainage.

The rôle of bronchoscopy in asthma is beneficial in some of the cases which have not responded to allergic desensitization. Relief is brought about in two ways: first, by physical drainage with removal of secretions and, second, by the preparation of autogenous vaccines with which patients are desensitized. The rôle here is secondary to that of the allergist. It is almost needless to say, however, that persistent wheeze is insufficient to make a diagnosis of asthma. There is no truer saying than all that "wheezes" is not asthma.

Tracheobronchitis in its chronic form is a frequent condition, in which the bronchi show definite inflammatory change with thickening of the spurs to the various bifurcations but show no dilatation when injected with lipiodol. Repeated aspiration may give relief from the cough and expectoration. Some cases may have definite wheezing, in which autogenous vaccine may be of value. Medication may be directly applied. In all of these conditions upper respiratory passages should not be neglected, especially the nasal accessory sinuses.

Foreign bodies are always to be held in mind in all cases with or without the history of aspiration.

Diseases of the oesophagus may produce symptoms referable to the

respiratory tract, due to the pressure on the posterior wall of the trachea from tumor, diverticula, foreign body, etc. Hypertrophy of the thyroid gland must be considered, as it, too, may produce constriction of the trachea or impingement on a bronchus.

As an aid to the thoracic surgeon the bronchoscopist may be of value in (1) diagnosis, (2) localization of the lesion, and (3) preoperative and postoperative aspiration of secretions.

Many cases previously diagnosed as postoperative pneumonia are in reality postoperative atelectasis, due to accumulated secretions of tenacious character (Tucker (11)). Immediate aspiration in these cases is very striking, and should always be thought of following all types of surgery whether with local or general anaesthesia.

Diseases of the larynx may be examined and treated satisfactorily with the same unit. Our experience has been chiefly with tuberculosis of the larynx, the results of which have been more than pleasing.

From an economic viewpoint the bronchoscopic clinic may be of great saving to the community, especially in municipal institutions, by reducing the hospitalization of many patients. More accurate and immediate diagnosis, as well as therapy, may be had.

Technique is an important item. The procedure requires some special training which is easily available. Certain equipment is necessary, plus an organized team in which assistants become familiar with the procedure. This is important, as colleagues must be convinced that the examination is not a trying ordeal for the patient and is free from danger.

Bronchoscopy is not a one-hundred per cent procedure in either diagnosis or treatment, but it must occupy a prominent place in diseases of the lungs, giving us more understanding and allowing us to think in terms of pathology of the tracheobronchial tree in a broader sense.

CONCLUSIONS

1. Bronchoscopy must be considered as a clinical necessity in diseases of the chest.
2. Chest groups should organize better bronchoscopic services.
3. Differential diagnosis is often dependent on bronchoscopy.
4. Economically, it will result in great savings to the community, because of reduction in hospitalization by more immediate and accurate diagnosis as well as treatment.
5. Great knowledge is to be gleaned by constant observation of the bronchi.

6. Tuberculosis not infrequently requires the same bronchoscopic aid as do polypi, stenoses, carcinomata, ulcerations, bleeding points, and bronchial obstructions.

7. Thoracic surgery may be greatly aided by bronchoscopy.

8. Every emphasis must be placed on the chronic cough and adequate treatment given before damage has been too extensive.

9. Prebronchiectatic conditions must be recognized and considered.

10. Tuberculosis of the larynx is easily treated by direct laryngoscopy.

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Discussion

(Dr. C. L. Jackson, Philadelphia)

Dr. Buckles has very well shown that bronchoscopy is indispensable in the diagnosis and treatment of diseases of the chest, including tuberculosis. One of the things that has retarded the development of bronchoscopic clinics in sanatoria is the supposed taboo on bronchoscopic examination of the tuberculosis patient. This taboo has now been discarded, and a number of institutions have reported bronchoscopic studies on sufficiently large series of tuberculous patients to prove that tuberculous infection *per se* is no contraindication to bronchoscopy. It is important to know whether or not the tuberculous patient has bronchial ulceration and whether or not he has an obstructive bronchial granuloma or tuberculoma. Bronchoscopy affords the only means of definitely determining these things. The effect of the presence of bronchial obstruction on the indications for thoracoplasty and other forms of collapse therapy is a very important, though unsettled, question, the answer to which will be known only after a sufficiently large number of patients have had pre- and postoperative bronchoscopic examinations.

Benign tumors of the bronchus, such as the one described by Dr. Buckles, are not infrequently found in patients previously diagnosed as tuberculous. Several of the patients in whom we have seen such tumors were referred from

sanatoria, where they had been under treatment for longer or shorter periods. All patients with haemoptysis but negative sputum should have a diagnostic bronchoscopy.

We have found that positive bronchoscopic biopsy will be obtained in about 75 per cent of the cases of bronchial carcinoma, but bronchoscopy is important in the negative cases also, in that it demonstrates the normality of the accessible bronchi. In some of the cases in which tissue for biopsy is not obtainable, indirect evidences may be obtained, such as rigidity or distortion.

I quite agree with Dr. Buckles's views on the treatment and prophylaxis of bronchiectasis. Certainly, some of the early cases will be checked by bronchoscopic treatment, especially if obstructing granulations or other obstructive factors can be found and eliminated.

Dr. Buckles has taken a very wise stand in connection with the treatment of pulmonary abscess. Patients with this serious condition should be treated early by medical and bronchoscopic measures rather than by surgery, but surgery should not be delayed beyond the optimum time for open drainage if they do not respond within a few weeks to more conservative measures.

Thoracic surgery has made marvelous progress in recent years, but it is interesting to note that thoracic surgeons to-day universally accept diagnostic bronchoscopy as a "necessity." A few years ago, Hudson of Detroit read a paper entitled *The Inseparability of Bronchoscopy and Thoracic Surgery*. Bronchoscopy is of value to the surgeon, not only as a preliminary diagnostic and therapeutic measure, but also during and after various operative procedures.

Lastly, as to the question of who should do bronchoscopy,—in a paper read last winter during the Post-Graduate Fortnight of the New York Academy of Medicine, I discussed this question, taking the view that while bronchoscopy was developed by the laryngologists, there is no reason why its present practice should be restricted to them. In some institutions all bronchoscopy will continue to be done by the laryngologist; in others it will be done by the thoracic surgeon or the internist. Every institution will have to work out its own solution. The important thing is that the indications for bronchoscopy be recognized, and that some one, properly trained, do the work in an efficient, safe and satisfactory way.

BRONCHOGRAPHY WITH IODIZED OIL NOT WITHOUT DANGER

Report of a Case

LOUIS SCHNEIDER[1] AND JACOB SEGAL[1]

Since lipiodol was introduced in 1922, it has attained an ever-increasing vogue for the delineation of bronchopulmonary pathological processes by X-ray. A patented preparation of 40 per cent iodine, chemically combined with an unsaturated oil (poppy-seed oil), its use in bronchography has become well-nigh universal. Attempts to displace this product by combinations of other oils with iodine or combinations of oil with other halogens (bromine) have been much less satisfactory, and, to date, workers in chronic pulmonary disease throughout the world rely mainly on lipiodol as the radiopaque medium for bronchography.

Except by the French, who discovered lipiodol, in the early days great caution was exercised in its use, the so-called well known deleterious effects of iodine in pulmonary tuberculosis serving as a deterrent to the use of iodized oil for diagnostic purposes in that disease. Then our rule was not to do a bronchogram until the presence of tuberculosis was ruled out by the exhibition of several negative sputa. As early as 1927, Archibald and Brown (1), who were among the first on this continent to use lipiodol in acid-fast lesions, reported a case of fatal tuberculous bronchopneumonia following an injection of lipiodol, which was done in those days by way of the bronchoscope. However, Singer and Francis (2) soon followed with a report of the use of this oil for bronchography in 277 cases, introducing it by the simple method of aspiration into the trachea. Of these cases, 35 had chronic pulmonary tuberculosis, and in none of these was there noted any serious after-effect as a result of this procedure. It is not stated, however, how long the latter group of cases were under observation subsequent to the procedure. Experimentally, the above workers find no cause for concern in using lipiodol, quoting Ballin to the effect that the injection of iodized oil into the bronchial tree

[1] Bronx, New York. From the Vanderbilt Tuberculosis Clinic and the Fordham Hospital Chest Clinic, New York City.

of a rabbit is not followed by any inflammatory reaction that can be demonstrated either microscopically or macroscopically.

Following upon this report, and despite instances of the spread of tuberculous lesions in the lung after the introduction of lipiodol (Amberson and others), bronchography in the presence of pulmonary tuberculosis is being done very extensively at present. Neuhof (3) even states that "a case of pulmonary tuberculosis is not completely studied for purposes of operation, if a bronchographic examination has not been made." Murphy (4) from the same institution feels that bronchography is an essential and safe adjunct in the study of pulmonary tuberculosis. The latter author reports 99 injections given in this disease with no major complications (length of follow-up is not mentioned). Like Forestier and Sicard, he recommends that lipiodol may be used in any case of pulmonary tuberculosis except the following: (1) acute pulmonary tuberculosis accompanied by fever; (2) debility of the patient; and (3) recent haemorrhage, in which case ten days must elapse before the procedure is undertaken.

Only recently, Cabitt, Singer and Graham (5) reported no serious effect after several years of the use of lipiodol in pulmonary tuberculosis, and highly recommend bronchography before and after thoracoplasty.

Lest from the foregoing, one feels that bronchography with iodized oil is a rather harmless procedure, we are reporting the following case, which, we think, illustrates more clearly than any other described in the literature or seen by us the possible danger in this procedure. Here we started out with apparently normal lungs as revealed by physical signs and X-ray, and, over a year after lipiodol was introduced into the bronchi, we had on our hands a full-blown case of pulmonary tuberculosis.

J. F.: age 52, born in Ireland, in the United States 8 years, never married, was a farmer and worked on the soil in his native country for about 30 years. Upon arrival here, he worked as a gardener for two years and then as a watchman for three years until he lost his job. There is no family or known contact history of pulmonary tuberculosis. He was first seen at the Vanderbilt Clinic in June, 1929, and was referred to the Presbyterian Hospital for an operation on hydrocele of the tunica vaginalis. At that time, he had no symptoms referable to the respiratory tract, and his lungs were clear on physical examination. A short time later, he was readmitted for operation on left inguinal hernia and left hydrocele.

From the follow-up surgical clinic, he was referred to Vanderbilt Tuberculosis Clinic on November 15, 1933, because of a persistent cough of a few

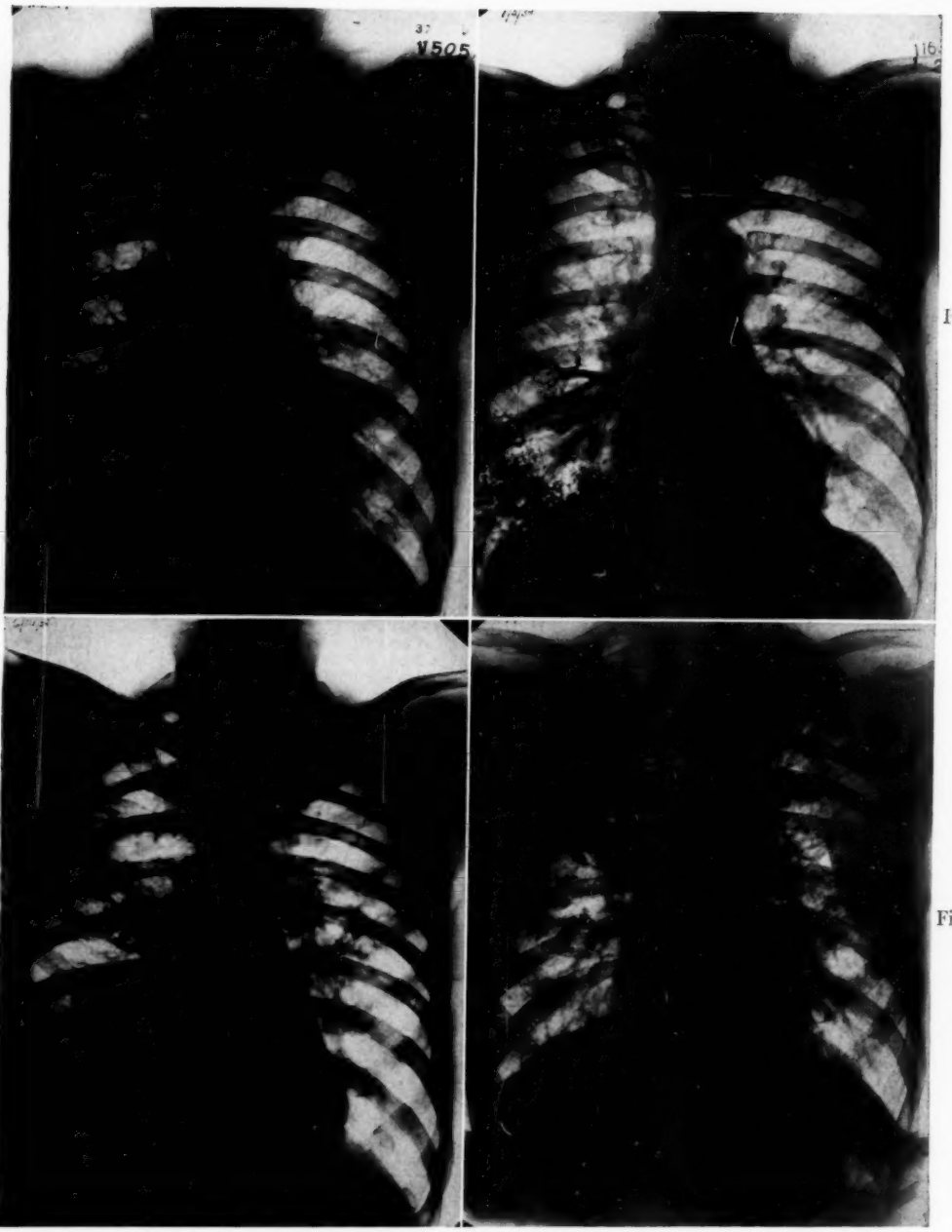

Fig. 1. November 15, 1933
Fig. 2. January 3, 1934
Fig. 3. June 21, 1935
Fig. 4. April 1, 1936

weeks' duration. This was productive of a small amount of nonbloody, nonodorous mucoid sputum. The patient also complained of some weakness. Examination of the chest revealed no abnormal lung signs whatever. An X-ray taken the same day (figure 1) showed no localized lesion, but the markings were increased in the right lung in its lower two-thirds, and the right root shadow was rather prominent. The rest of the examination was irrelevant. The sputum was reported negative on two occasions as was the Wassermann.

A preliminary suspicion of bronchiestasis was entertained because of X-ray findings and respiratory symptoms in the presence of negative sputum. A lipiodol bronchogram was therefore done, January 3, 1934 (figure 2), the oil being injected through a tracheal cannula by the well known supraglottic route the effort being made to produce a right sided bronchogram. Though the picture was interpreted by some as evidence of slight cylindrical dilatation in the right middle lobe, we felt that there was little bronchiectasis to speak of. Nevertheless, another bronchogram was done, June 23, 1934, some of the oil entering the bronchi at a higher level on the right side, but no appreciable difference from the previous X-ray was discernible. Within two days after the last lipiodol injection, the patient developed a coryza and complained of swollen eyelids, a typical case of iodism. Except for the slight relief the patient got following these bronchographic procedures, he continued to complain of cough and expectoration, though weight and strength were unimpaired.

A little blood-streaking began to be noted late in 1934 and early in 1935, but physical examination of the chest and examination of the sputum continued to be negative. In May, 1935, evidence of a chronic pansinusitis was found, and the patient began to receive treatment for the condition by the Nose and Throat Department at Vanderbilt Clinic. Shortly afterward, the patient moved from the Clinic district, and reappeared at Fordham Tuberculosis Clinic on June 20, 1935. His symptoms were practically unchanged, except that he streaked a little more. His weight at that time was 137 pounds; temperature was normal; pulse was 120. He hardly appeared ill. Physical examination of the chest was negative, but an X-ray taken the following day, June 21, 1935 (figure 3), showed an exudative process in the 3rd interspace on the right side more or less surrounding an area of retained lipiodol. In addition, a small effusion was noted at the right base and suspicion of early lesion in the 3rd interspace, left side, adjacent to the hilum. The sputum taken then was reported positive. Before the sputum report came back, the patient was lost track of, until he presented himself again at Fordham Tuberculosis Clinic on April 1, 1936. His story then was that the cough and expectoration were unchanged, but that he was now being annoyed by more frequent blood-spitting, the last such episode having occurred six weeks previously. There was increasing dyspnoea; but no fever, sweats or chest pain were noted, however, and he was no weaker than when he first began to

be harassed by respiratory symptoms. His appetite was good, but he was extremely nervous, sleepless and restless of late.

Physical examination of the chest revealed evidence of a good deal of moisture in the right upper half of the lung, and less marked in the left upper lobe. There was no doubt in the mind of the examiner that he was dealing with a case of advanced bilateral pulmonary tuberculosis. An X-ray taken the same day, April 1, 1936 (figure 4), confirmed this opinion and also showed remnants of retained lipiodol in the right side. The sputum came back positive. It was interesting to note that the patient, in spite of the advancement of the lesion had gained seven pounds since the previous visit in June, 1935. He was also afebrile and looked no sicker than when first examined for pulmonary symptoms over two and a half years ago.

Comment

As far as we know, there has been no reported instance of pulmonary tuberculosis following the injection of lipiodol into the bronchi of apparently normal lungs. That there is a causal relation between the development of clinical tuberculosis and the presence of iodized oil in the lower respiratory system is evident in an examination of figure 3. Here you see the exudative process originating in immediate proximity to the retained oil, looking very much as if there were here a reaction to the presence of a foreign body.

Sweany (6) has shown that many a small encapsulated focus containing tubercle bacilli will not be seen by X-ray, although autopsy examination reveals it macroscopically with ease. He also points out that our present technique is not developed enough for roentgen delineation of small early lesions. It is very possible that such an invisible encapsulated focus existed in this patient's right lung at the time of the first chest examination, and that the prolonged presence of lipiodol reactivated this nonclinical process and converted it into manifest disease.

It has been the experience of others who practice this procedure extensively as well as ourselves, that, after bronchography, the iodized oil disappears from the pulmonary system within a few weeks at the most; only occasionally is it retained a few months; rarely more than a year. Most of the oil is got rid of in the expectorated sputum, but just a little is absorbed into the circulation. Bernard (7) reports a case in which lipiodol was seen on X-ray of the chest one year after bronchography for bronchiectasis of the left lower lobe. He believes, and we agree, that this is an unusual persistence, but he states that the continued presence of lipiodol in the lower respiratory tract is no cause for

worry. Our case is remarkable in that oil is still noted about two years after lipiodol was injected into the right bronchial tree and also that clinical tuberculosis developed more than a year after bronchography, the process starting around an area of retained lipiodol.

It is possible that Graham, Singer, Neuhof and others have seen no ill effects following bronchography with iodized oil since many of their cases may not have been followed for a long time after this procedure was done. Also, their patients may have got rid of their lipiodol quickly enough not to evoke additional damage to the already diseased lungs. It is possible that, with everyone "running riot" with this diagnostic method in the presence of bronchopulmonary disease, other cases, similar to the one here reported, will appear in the literature in the near future.

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not clinch the diagnosis, bronchoscopy should not be deferred too long, as it may immediately give us the true pathological condition.

We prefer not to bronchoscope in the presence of active haemorrhage or immediately following it, unless indications of obstruction are present. In no case have we seen any evidence that harm was done to the tuberculous process.

ERRATUM

Volume XXXV, No. 4, April, 1937

Page 585: **Because of printer's error the illustration on page 585 was printed in one color only, instead of two colors. Substitute pages 585–586 herewith for the corresponding pages in the April 1937 issue.**

AUTHORS' ERRATUM SLIP

Volume XXXV, No. 4, April, 1937

In their article on "The Frequency of Artificial-Pneumothorax Refills in Tuberculosis" the authors, R. Maxwell Franklin, William A. Zavod and Horacio E. Perez, wish to make the following change and correction:

On page 526, second paragraph, third line: *60 per cent Moderately Advanced and 40 per cent Far Advanced* should read *39 per cent Moderately Advanced and 60.9 per cent Far Advanced.*

obstructive emphysema. This benign tumor was removed with biopsy forceps and the stump cauterized with 50 per cent silver nitrate. No recurrence. (Fig. 8.)

Fig. E. Papillary carcinoma of the right common bronchus at the junction of the upper lobe. (Fig. 11.)

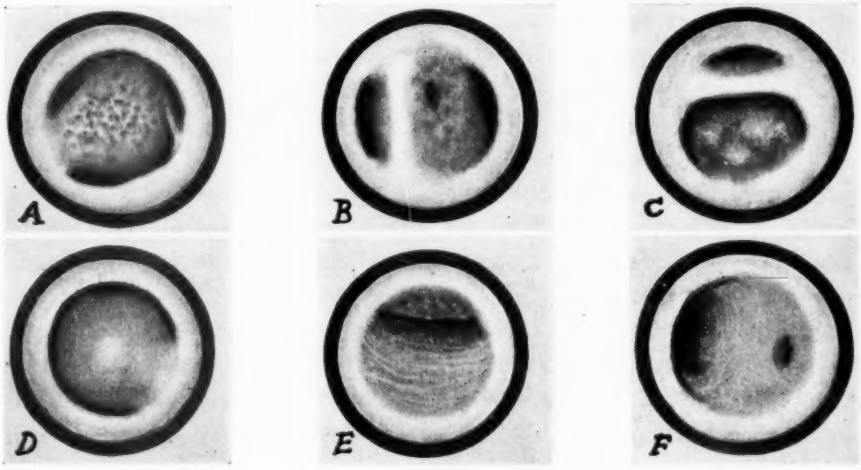
Fig. F. Ulceration on the lateral wall of the right descending bronchus. (Fig. 12.)

Note: All tumors proved by biopsy.

Bronchiectasis is becoming such a problem in chest clinics, due to its high incidence and morbidity, that it is demanding much attention. We consider most all cases as obstructive, and perhaps know something of the mechanisms producing the disease, though much is yet to be learned. The bronchoscope has and will throw much light on this problem. I feel that the proper approach is from a prophylactic viewpoint,

not clinch the diagnosis, bronchoscopy should not be deferred too long, as it may immediately give us the true pathological condition.

We prefer not to bronchoscope in the presence of active haemorrhage or immediately following it, unless indications of obstruction are present. In no case have we seen any evidence that harm was done to the tuberculous process.



Bronchoscopic Views

The above represent the gross views as seen through the bronchoscope on six of the previous X-ray films.

Fig. A. Squamous-cell carcinoma of the right descending bronchus, showing complete obstruction of the lower lobe and partial obstruction of the middle lobe.

Fig. B. Represents tuberculous granulations of the right common bronchus, with ulceration just below the bifurcation of the trachea on the medial wall. (Fig. 4.)

Fig. C. Adenocarcinoma of the right lower lobe producing atelectasis. (Fig. 5.)

Fig. D. A round smooth glistening adenoma of the right common bronchus producing obstructive emphysema. This benign tumor was removed with biopsy forceps and the stump cauterized with 50 per cent silver nitrate. No recurrence. (Fig. 8.)

Fig. E. Papillary carcinoma of the right common bronchus at the junction of the upper lobe. (Fig. 11.)

Fig. F. Ulceration on the lateral wall of the right descending bronchus. (Fig. 12.)

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Bronchiectasis is becoming such a problem in chest clinics, due to its high incidence and morbidity, that it is demanding much attention. We consider most all cases as obstructive, and perhaps know something of the mechanisms producing the disease, though much is yet to be learned. The bronchoscope has and will throw much light on this problem. I feel that the proper approach is from a prophylactic viewpoint,

that is, properly recognizing the chronic cough, sinus pathological conditions, etc., alleviating, if possible, any basis for the formation of the disease. Prebronchiectatic phases should be borne in mind constantly. Early dilatation and aspiration of the bronchi may greatly facilitate emptying power, and at the same time removal of the obstruction may be affected.

Proper treatment and consideration of the cough so often following acute infectious diseases in children (Tucker (8)) cannot be overemphasized. This early thickened, inflamed, swollen bronchus of infancy, if neglected, may be the chief fundamental factor in the mechanism of bronchiectasis later in life. In the advanced cases, repeated aspiration may give much temporary relief. We feel as Ballon (9) does, that the progress of the disease may be checked in some cases. Relief of toxaemia is noticeable. Retardation of the secondary degenerative changes of other organs and lessening of the probabilities for recurrent bronchopneumonia should follow.

Pulmonary abscess, if obtained early, may be satisfactorily treated. Our experience leads us to believe that the time element is all important. Clerf (10) has shown that 70 per cent of early cases were cured. Bronchoscopy should not be carried past the optimum time for open drainage.

The rôle of bronchoscopy in asthma is beneficial in some of the cases which have not responded to allergic desensitization. Relief is brought about in two ways: first, by physical drainage with removal of secretions and, second, by the preparation of autogenous vaccines with which patients are desensitized. The rôle here is secondary to that of the allergist. It is almost needless to say, however, that persistent wheeze is insufficient to make a diagnosis of asthma. There is no truer saying than all that "wheezes" is not asthma.

Tracheobronchitis in its chronic form is a frequent condition, in which the bronchi show definite inflammatory change with thickening of the spurs to the various bifurcations but show no dilatation when injected with lipiodol. Repeated aspiration may give relief from the cough and expectoration. Some cases may have definite wheezing, in which autogenous vaccine may be of value. Medication may be directly applied. In all of these conditions upper respiratory passages should not be neglected, especially the nasal accessory sinuses.

Foreign bodies are always to be held in mind in all cases with or without the history of aspiration.

Diseases of the oesophagus may produce symptoms referable to the

A SUMMARY OF THE RESULTS OF GROUP TUBERCULIN-TESTING WITH P.P.D. (PURIFIED PROTEIN DERIVATIVE) IN THE UNITED STATES

Final Report of the National Tuberculosis Association

JESSAMINE S. WHITNEY AND ISABEL McCAFFREY

INTRODUCTION

The development of a nonsensitizing standardized tuberculin, P.P.D. (Purified Protein Derivative), with a standard procedure for the performance and interpretation of tuberculin tests, made it possible to conduct this survey of tuberculous infection in the United States. The results of group testing with MA-100, the first standardized tuberculin to be recommended for trial by the Committee on Medical Research of the National Tuberculosis Association, were published early in 1936 (1), and are still valid as a measure of tuberculous infection in groups studied for the first time. However, because of the possibility of MA-100 itself sensitizing children (2), and in view of the advisability of keeping the results of tuberculin testing aligned with those obtained with Old Tuberculin in the past (3), the National Tuberculosis Association discontinued the distribution of MA-100 in June, 1934. At the same time, under the direction of the Tuberculin Committee, a subcommittee of the Committee on Medical Research, P.P.D. was offered for sale at a reduced price for group testing. It is to Dr. Florence B. Seibert of the Henry Phipps Institute (4) that we are indebted for the development of P.P.D., a product that does not have the objectionable qualities of MA-100 but is like MA-100 in that it is a stable tuberculin that can be reproduced in an exact strength.

The purchase of P.P.D. at a low price carried with it the obligation to return reports to the National Tuberculosis Association for statistical analysis. In this way, during the two-year period following June, 1934, reports were received for 85,709 first- and second-strength tests among 56,688 individuals. This number was thought to be sufficiently large and comprehensive to be used as a basis for valid conclusions, and the group tests were summarized with the result that the individual differences of single groups were minimized. This was made possible by the use of a standard tuberculin with uniform dosage, technique and inter-

pretation. This report presents the findings of a statistical study of the combined groups.

The standard procedure required an intracutaneous injection of 0.1 cc. of first-strength tuberculin containing 0.000,02 mgm. of P.P.D. In the case of negative reactions, the first injection was to be followed by an injection of 0.1 cc. of second-strength tuberculin containing 0.005 mgm. of P.P.D. If no reaction occurred within forty-eight hours of either injection, the test was interpreted as negative. Unfortunately, the instructions as to the use of first- and second-strength tuberculin were not uniformly followed. Of the 56,688 persons included in this survey, 3,071 were tested with second-strength tuberculin only. The remaining 53,617 persons were tested with first-strength tuberculin, and only 29,021, or 75 per cent, of the 38,829 negative reactors, were retested with second-strength tuberculin. Nevertheless, all of these reports were thought to be of value in arriving at a reliable index of tuberculous infection in the United States, and therefore have been included in the statistical study.

A classification of the 56,688 persons tuberculin-tested according to age disclosed the fact that boys and girls between ten and nineteen years of age comprised almost two-thirds of the groups reported. Only 15 per cent of the number tested were twenty years of age or over, whereas 60 per cent of the population of the United States belonged in that classification at the time of the last census. Since the groups tested also contained a larger proportion of colored and native-born persons than did the population of the United States in 1930, the combined groups under study could not be used as a representative sample of the population of the United States. It was therefore decided to approach a reliable index of tuberculous infection in the United States by adjusting the infection rates obtained according to the age, color, and nativity classifications of the population of the United States in 1930. The rates found for each classification in the groups tuberculin-tested were weighted according to the percentage distribution of those classifications of the population in the United States in 1930. The adjusted percentage of positive reactors for the entire number tested was found to be higher than the non-adjusted rate because of the added importance given to the adults and persons of foreign extraction in the groups tested. The incidence of infection was found to be high in both of those groups which were not very well represented in the groups studied. The adjusted infection rates are representative of the general population and are the ones to be quoted for the United States. They are presented in the following tables

for those classifications for which adjustments could be made. The specific (nonadjusted) rates also appear for comparison.

ANALYSIS OF DATA

Size of dose: The percentage of positive reactors found among the 56,688 persons tested with either first- or second-strength P.P.D. was 36.4, as shown in table 1. There were 53,617 tests made with first-

TABLE 1

Summary of the results of group tuberculin-testing with P.P.D. in the United States, 1934–1936

STRENGTH OF TUBERCULIN USED AND COLOR OF PERSONS TESTED	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
1st and/or second strength:			
Total	56,688	20,607	36.4
White	41,493	11,959	28.8
Negro	7,823	3,389	43.3
Indian	7,159	5,185	72.4
Other colored	213	74	34.7
1st strength:			
Total	53,617	14,788	27.6
White	38,573	7,607	19.7
Negro	7,681	2,495	32.5
Indian	7,154	4,622	64.6
Other colored	209	64	30.6
2nd strength following negative reaction to 1st strength:			
Total	29,021	4,903	16.9
White	22,641	3,513	15.5
Negro	3,924	825	21.0
Indian	2,408	559	23.2
Other colored	48	6	12.5
2nd strength only (No test with 1st strength given):			
Total	3,071	916	29.8
White	2,920	839	28.7
Negro	142	69	48.6
Indian	5	4	80.0
Other colored	4	4	100.0

strength tuberculin, 27.6 per cent resulting in positive reactions. Of the 29,021 negative reactors to first-strength tuberculin who received tests with second-strength tuberculin, 16.9 per cent showed positive reactions to the second test. However, there were 9,808 negative reactors to first-strength tuberculin who failed to receive second injections of second-strength tuberculin. Assuming that these would have shown positive reactions to second-strength tuberculin in the same proportion as those

who did receive second-strength tests, there are at least 1,500 undiscovered positive reactors because of the failure to complete tests with second-strength tuberculin.

The Negroes and Indians were more sensitive to P.P.D. than were the

TABLE 2

Number of persons included in a study of group tuberculin-testing with P.P.D. in the United States according to color, by states, 1934–1936

STATE	NUMBER TESTED				
	Total	White	Negro	Indian	Other colored
All states	56,688	41,493	7,823	7,159	213
Arizona	3,918	72	—	3,846	—
Arkansas	2,211	1,544	667	—	—
California	7,435	6,997	232	16	190
Colorado	1,691	1,683	8	—	—
Connecticut	44	44	—	—	—
District of Columbia	218	—	218	—	—
Florida	113	113	—	—	—
Georgia	4,488	2,447	2,039	—	2
Idaho	129	128	—	—	1
Illinois	833	831	2	—	—
Indiana	2,739	2,678	61	—	—
Iowa	632	624	8	—	—
Kansas	1,741	1,683	41	14	3
Louisiana	2,019	1,497	518	—	4
Maryland	187	67	120	—	—
Michigan	2,492	2,467	25	—	—
Minnesota	505	500	—	5	—
Mississippi	278	—	278	—	—
Nebraska	1,393	1,333	60	—	—
Nevada	65	—	—	65	—
New Jersey	206	171	35	—	—
New Mexico	4,077	920	3	3,152	2
New York	283	280	3	—	—
Ohio	5,213	4,484	728	1	—
Oregon	638	631	1	—	6
Pennsylvania	8,379	7,461	916	—	2
South Carolina	100	100	—	—	—
Texas	405	327	78	—	—
Utah	2,169	2,106	—	60	3
Virginia	1,434	45	1,389	—	—
West Virginia	653	260	393	—	—

white persons tested. Of the white positive reactors in the groups that were tested with second-strength tuberculin following negative reactions to tests with first-strength tuberculin, 68 per cent were detected with first-strength tuberculin, compared with 75 per cent for the Negroes and 89 per cent for the Indians.

Geographic areas: Thirty states and the District of Columbia are represented in the entire study as shown in table 2. The largest number of reports for tuberculin tests among white persons came from Pennsylvania. Georgia reported more tests among Negroes than any other state; Arizona and New Mexico contributed 98 per cent of the reports for the Indians tested with P.P.D.

With the exception of the resort area, the states along the Eastern coast showed the greatest evidence of tuberculous infection, whereas the lowest percentage of positive reactors was found among the groups in the Central states. The number of persons tested in each area is not large enough to establish conclusive evidence concerning the prevalence of tuberculous infection in each section. However, it is interesting to note that the results of this study are in agreement with those found among students tested in colleges throughout the United States (5).

TABLE 3

Results of group tuberculin-testing with P.P.D. in the United States, from 1934 to 1936 by geographic areas

AREA	NUMBER TESTED	PER CENT POSITIVE
United States	56,688	36.4
New England	44	38.6
Middle Atlantic	8,868	40.2
East North Central	11,277	29.3
West North Central	4,271	23.8
South Atlantic	7,193	39.3
East South Central	278	33.1
West South Central	4,635	23.4
Mountain	12,049	52.7
Pacific	8,073	29.0

Type of group: More than 18 per cent of those tested with P.P.D. were high-school students; 17 per cent were college students; 12 per cent were elementary school pupils; and 13 per cent came from clinics. Another 13 per cent were Indians, and less than 1 per cent were teachers, nurses and doctors. The remaining 27 per cent came from miscellaneous or unclassified groups. Excluding the Indians reported, the highest infection rate was found among the 7,106 persons tested in clinic groups, with 53.2 per cent showing positive reactions to either first- or second-strength P.P.D. The lowest percentage of positive reactors, 18.5, was found among the 6,622 elementary school children in the groups tested.

Urban and rural: Tuberculin tests among 32,477 individuals were reported either typically urban or typically rural. Of the 22,688 persons classified as urban residents, that is, living in places with a population of over 2,500, 33.6 per cent were found to be positive reactors to either first- or second-strength P.P.D. There were 9,789 individuals included in the study of rural groups, of which 21.4 per cent evidenced tuberculous infection. For both sexes, and males and females taken separately, the percentage of positive reactors among the urban groups was more than 10 per cent higher than that found among the rural groups.

Age: The percentage of positive reactors among the combined groups adjusted for age, color, nativity and parentage was 47.0. The reports included in this study indicated that there were fewer positive reactors proportionately among the children six years of age than there were at any other year of life. Following the sixth year of life, the percentage of positive reactors increased with age at an average rate of over one per cent for every year of life up to the age of 20. The proportion of positive reactors among the adults 20 years of age and over included in the groups tuberculin-tested was 34 per cent higher than that found among the boys and girls reported under 20 years of age.

TABLE 4

Results of group tuberculin-testing with P.P.D. in the United States according to age, 1934–1936

AGE	NUMBER TESTED	PER CENT POSITIVE	PER CENT POSITIVE ADJUSTED FOR COLOR, NATIVITY AND PARENTAGE
All ages	56,688	36.4	47.0*
Under 5	1,450	24.6	24.9
5–9	9,367	23.3	21.6
10–14	17,598	33.4	28.4
15–19	18,943	36.3	31.9
20 and over	8,692	58.3	60.1
Age unknown	638	—	—

* Adjusted for age as well as color, nativity, and parentage.

Contact and noncontact: Almost 15 per cent of the total number tested were reported to have had some definite contact with tuberculosis. The percentage of positive reactors among them was 54.2, whereas only one-third of those for whom no history of contact with tuberculosis was reported showed evidence of tuberculous infection. The infection rate indicated for contacts under five years of age was three times that found

for noncontacts in the same age-group. However, the disparity between the infection percentages for the two groups became progressively less as age increased, due to the fact that the proportion of positive reactors increased with age generally at a more rapid rate among the noncontacts than among the contacts.

TABLE 5

Results of group tuberculin-testing with P.P.D. in the United States among contacts and noncontacts, by age, 1934–1936

AGE	CONTACTS		NONCONTACTS	
	Number tested	Per cent positive	Number tested	Per cent positive
All ages	8,276	54.2	48,412	33.3
Under 5	608	40.3	842	13.2
5–9	1,685	43.5	7,682	18.9
10–14	2,474	50.8	15,124	30.6
15–19	1,846	54.1	17,097	34.4
20 and over	1,575	77.1	7,117	54.2
Age unknown	88	—	550	—

Sex: Approximately the same number of males and females were reported to have had tuberculin tests with P.P.D. The males showed a slightly higher percentage of positive reactors than did the females, the adjusted rate for males being 48.3 and that for females 45.9 per cent. A higher infection rate was found among girls 5 to 9 years of age than among boys of the same age, but in every other age-group there was a greater proportion of male positive reactors than female positive reactors of the same age.

TABLE 6

Results of group tuberculin-testing with P.P.D. in the United States according to age and sex, 1934–1936

AGE	MALE			FEMALE		
	Number tested	Per cent positive	Per cent positive adjusted for color, nativity and parentage	Number tested	Per cent positive	Per cent positive adjusted for color, nativity and parentage
All ages	28,378	37.8	48.3*	28,310	34.9	45.9*
Under 5	723	24.6	25.5	727	24.5	24.3
5–9	4,548	23.8	21.2	4,819	22.8	22.1
10–14	8,614	34.8	29.4	8,984	32.1	27.6
15–19	9,661	37.8	34.2	9,282	34.7	29.8
20 and over	4,534	59.7	61.4	4,158	56.9	58.6
Age unknown	298	—	—	340	—	—

* Adjusted for age as well as color, nativity and parentage.

White and Negro: White persons comprised 74 per cent of the entire number included in this study, and the percentage of positive reactors among them adjusted to the population of the United States in 1930 was 46.5. The Negroes tested showed only one per cent more positive reactors in proportion to their numbers than did the whites, the infection rate for the Negroes adjusted for age being 47.8 per cent. The non-adjusted rate for the whites tested was 15 per cent lower than that found for the Negroes, because of the small proportion of adults and foreign-born included in the groups tested. The Negro infection rates were higher than the white rates in almost every age-group, with the exception of the group 20 years of age and over.

However, the trend of infection among the Negroes tested increased with age up to the age of 20 at an average rate of one-half of one per cent for every year of life, as compared with an average increase of one per cent for every year of life among the white persons in the groups studied.

TABLE 7

Results of group tuberculin-testing with P.P.D. in the United States among Whites and Negroes, by age, 1934–1936

AGE	WHITE			NEGRO		
	Number tested	Per cent positive	Per cent positive adjusted for nativity and parentage	Number tested	Per cent positive	Per cent positive adjusted for age
All ages	41,493	28.8	46.5*	7,823	43.3	47.8
Under 5	1,099	22.7	24.1	283	29.7	—
5–9	6,937	17.1	20.5	848	25.1	—
10–14	12,766	24.2	26.7	1,766	36.4	—
15–19	14,377	28.4	29.8	2,525	41.6	—
20 and over	5,900	55.2	59.6	2,324	59.1	—
Age unknown	414	—	—	77	—	—

* Adjusted for age as well as nativity and parentage.

Nativity and parentage: Of the 41,493 white persons included in the groups studied, 38,806 reported both their own and their parents' nativity. There were 31,318 native-born of native parentage, 6,674 native born of foreign or mixed parentage, and 814 foreign-born. The highest percentage of positive reactors, 61.2, was found among those of foreign birth. The percentage of positive reactors among the native-born of foreign extraction was 38.4, whereas only 27.6 per cent of the native-born of native parentage evidenced tuberculous infection.

In the cases of foreign or mixed parentage, the father's country of birth was tabulated except when the father was native-born, in which case the mother's country of birth was tabulated. The parents of the 6,674 native-born Americans of foreign parentage were born in 54 countries in Europe, Africa, Asia, and South America, as well as Mexico and Canada, but more than 90 per cent of them were born in Canada, Mexico and the 19 European countries listed in table 8. Parents of 50 or more of the native-born Americans of foreign or mixed parentage were born in each of those 21 countries. Excluding those of Lithuanian descent, among whom only 56 tests were made, the highest proportion of positive reactors, 49.1, was found among the 576 children of Mexican parentage. Those of Russian descent came next with 48.2 per cent of the 371 tested evidencing tuberculous infection. The native-born of Hungarian parentage showed the least evidence of tuberculous infection, with 22.9 per cent of the 219 tested showing positive reactions to P.P.D.

Two-thirds of the 814 foreign-born persons included in the groups tested came from the seven countries listed in table 8. The proportion of positive reactors among them was 14 per cent higher than the adjusted infection rate computed for all of the combined groups under study. Unfortunately, the number reported for each country was too small for valid conclusions, but a notably higher infection rate was indicated for the foreign-born from the European countries listed than for those removed from the same country by one generation. More interesting and significant findings would probably result from a more extensive study of tuberculous infection in the groups of foreign extraction in the United States.

Indian: Ninety-eight per cent of the 7,159 Indians tuberculin-tested were reported by Dr. L. R. Jones of the U. S. Indian Service. The percentage of positive reactors among them was 72.4, an infection rate over 25 per cent higher than the adjusted rate found for the combined groups of all ages, colors, and races included in this study. Classifying the results of the P.P.D. tests among the Indians by age, the lowest percentage of positive reactors was found among the 62 children under five years of age. More than half of the Indians tested were found to be positive reactors at every age after the seventh year of life, and nine out of every ten tested at 20 years of age and over showed evidence of tuberculous infection.

The number of reports received for other than whites, Negroes and Indians was too small for statistical analysis. The majority of them

TABLE 8

Results of group tuberculin-testing with P.P.D. in the United States according to nativity and parentage, 1934–1936

NATIVITY AND PARENTAGE	NUMBER TESTED	PER CENT POSITIVE
Native born of foreign or mixed parentage	6,674	38.4
Country of birth of parents		
Austria	270	36.3
Canada	305	32.5
Czechoslovakia	205	33.7
Denmark	124	28.2
England	334	30.2
Finland	209	32.1
Germany	398	33.2
Greece	65	36.9
Holland	626	33.7
Hungary	219	22.9
Ireland	172	41.9
Italy	1,327	46.6
Lithuania	56	55.4
Mexico	576	49.1
Norway	105	25.7
Poland	243	33.7
Russia	371	48.2
Scotland	128	27.3
Sweden	271	39.5
Switzerland	80	40.0
Yugoslavia	67	31.3
All others	523	36.3
Foreign born	814	61.2
Country of birth		
Canada	123	31.7
England	28	50.0
Holland	29	41.4
Italy	165	83.0
Mexico	76	55.3
Russia	90	97.8
Sweden	25	76.0
All others	278	52.9

were Chinese and Japanese, and the percentage of positive reactors among them was 34.7.

SUMMARY

The following significant findings are based upon a total of 85,709 group tuberculin tests with first- and second-strength Tuberculin, P.P.D. (Purified Protein Derivative) among 56,688 individuals in thirty states and the District of Columbia.

The use of P.P.D., which is a standardized nonsensitizing tuberculin, with instructions for uniform dosage and technique, made it possible to obtain more reliable and complete data than heretofore. The group tests were combined, with the result that the individual differences of single groups were minimized. A more reliable index of tuberculous infection in the United States was also approached by adjusting the infection rates for age, color, nativity and parentage according to the distribution of the population of the United States at the time of the last census in 1930. The adjusted rates are the ones to be quoted for the general population.

1. The adjusted percentage of positive reactors among the 56,688 persons of all ages included in this study was 47.0. The adjusted rate was 10 per cent higher than the nonadjusted rate because of the small proportion of adults and persons of foreign extraction included in the groups tested.

2. There were fewer positive reactors proportionately among the six-year-old children tested than there were at any other age. Following the sixth year of life, the trend of infection was generally upward at an average rate of over one per cent for every year of life up to the age of 20.

3. Adults, 20 years of age and over, included in the groups tested, evidenced 34 per cent more tuberculous infection than the total number of boys and girls reported under 20 years of age.

4. The percentage of positive reactors found among the 8,276 persons reported to have had contact with tuberculosis was 54.2, whereas only 33.3 per cent of those with no history of contact responded with positive reactions to P.P.D. The infection rate indicated for the contacts under five years of age was three times that for noncontacts in the same age-group, but the proportion of positive reactors increased with age, generally at a more rapid rate among the noncontacts than among the contacts.

5. Reports were received for almost the same number of males and females. The adjusted percentage of positive reactors for males was 48.3 as compared with 45.9 for females. There was a larger proportion

of male than female positive reactors to P.P.D. at almost every age-group.

6. The percentage of positive reactors among the white persons in the groups studied adjusted for age, nativity, and parentage was 46.5. The Negroes tested showed only one per cent more positive reactions proportionately than did the whites, the infection rate for the Negroes adjusted for age being 47.8 per cent. The nonadjusted rate for whites was 15 per cent lower than that found for Negroes, but the adjusted rate represents more closely the prevalence of infection in the general population. However, the trend of infection among the Negroes increased with age up to the age of 20 at a faster rate than that among the whites included in the reports studied.

7. Nativity and parentage seemed to be a significant factor in tuberculous infection among the white persons tested. Of the 31,318 native-born Americans of native parentage, 27.6 per cent evidenced tuberculous infection, whereas 38.4 per cent of the 6,674 native-born of foreign stock and 61.2 per cent of the 814 foreign-born responded with positive reactions.

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SIMILARITIES IN THE MANIFESTATIONS OF LEPROSY AND TUBERCULOSIS[1]

FREDERICK A. JOHANSEN[2]

In speaking of similarities in the manifestations of leprosy and tuberculosis, one is speaking of a parallelism that is real. The resemblance, as Denney and Ritter (1) have well said, "is not only from the clinical and pathologic standpoints, but in the historical, social, economical, climatological, epidemiological, laboratory and medical aspects, as well as in the treatment."

The causative organisms are related. Morphologically, both are rod-shaped organisms, similar in length, non-spore-bearing, each enclosed in a waxy capsule, and markedly pleomorphic. Physically, both show a high degree of resistance to cold and most external influences, but succumb to high temperatures and are readily destroyed by direct sunlight. Chemically, both organisms are acid-fast and gram-positive, and very sensitive to the action of chemicals such as carbolic acid and mercuric chloride. The essential chemical differences are the relatively higher water content of the tubercle bacillus and the comparatively larger quantities of lecithin and cholesterol in the lepra bacillus (2). The organisms show similarity from the standpoint of persistence within the human body; it is problematical in the case of both organisms whether, once established in the body, they are ever totally eliminated. The cultural comparison shows that, while the tubercle bacillus can be cultivated on suitable media, it is doubtful whether the lepra bacillus ever has been grown in cultures. It is true that acid-fast organisms have been cultivated from leprous lesions, but we still await the satisfactory fulfillment of Koch's postulates.

In the matter of virulence, it may be said that the lepra bacillus seems to be less destructive to human tissue than the tubercle bacillus or else the human organism is better prepared to resist its onslaughts, since

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the leprous lesion contains an immensely larger number of bacilli than does a lesion of tuberculosis comparable in size and in amount of tissue destruction.

Although our inability to cultivate *Mycobacterium leprae* and the lack of success attending animal inoculation have made it impossible to study more directly the toxic action of this microörganism, there is, nevertheless, some evidence which points toward the production of toxin by the bacillus. Of importance, both in demonstrating the probability of the existence of a definite toxin as well as indicating the close relationship between the lepra bacillus and the tubercle bacillus are the studies of the action of tuberculin upon leprous patients (3). When tuberculin is administered to lepers, a febrile reaction occurs usually within twenty-four or more hours after the administration. The fever differs from that produced by the use of the same substance in tuberculous patients in that it is of later occurrence and lasts considerably longer.

There is a lack of unanimity of opinion as to the frequency of occurrence and the significance of the true positive tuberculin reaction in leprosy. Some investigators believe that a positive reaction indicates infection with the tubercle bacillus, in lepers as well as in nonlepers. Dubois (4) did not find more positive reactors among lepers than among a comparable healthy population. His work was carried out in the Congo region. Wayson (5) found reactions less frequent among leprous patients in Hawaii than in control groups of the general population, and he also found evidence of clinical tuberculosis in a higher percentage of the positive leper reactors than among the positive reactors in control groups.

With such similarity between the causative agents of tuberculosis and leprosy it is not surprising to find similarities in the modes of infection in the two diseases. It is now generally agreed that in both diseases frank manifestation of the infection depends on constitutional and conditional factors. In leprosy as well as in tuberculosis, susceptibility to the initial infection is greatest in children, while adults are relatively less prone to acquire either disease. Direct inheritance is rare in both diseases. Removal of children as soon as practicable after birth from homes where open infection is present is looked upon as one of the most effective means of combating the extension of both tuberculosis and leprosy. It appears that children become infected with tuberculosis at an earlier age than with leprosy; for, whereas it is necessary to

remove the baby from the mother with open tuberculosis practically at birth, the need for this early separation does not appear to be so urgent in the case of the baby born to the leprous mother. Denney and Ritter (1) explain this difference by the greater dissemination of the tubercle bacillus and its more direct entrance into the human body through the respired air and in food. The marital infection rate is low in leprosy as in tuberculosis. There are many records of wives having lived intimately with leprous husbands and husbands with leprous wives for many years without acquiring the disease. Puberty is the age at which childhood infection is first likely to become manifest in both diseases.

The social problem presented by leprosy is similar in many respects to that presented by tuberculosis. The causative agents are most likely to become active in the individual of weak constitution who is in an ill-nourished and otherwise "run-down" condition, affected by grief, worry, overwork, overstudy, alcoholic and venereal excesses, or who has been weakened by having passed through an infectious illness. Bad housing and poor hygiene generally, and especially conditions of dampness, favor the development of leprosy, as of tuberculosis. The problem of control represents similarities. In each disease there is the need to search for contacts when a fresh case is discovered, to examine members of the household at intervals over a number of years, and to follow the children up through the years of adolescence.

Each of the two organisms has favorite tissues for its habitat, though the invasion of other tissues may take place. The favorite habitat of the leprosy bacillus is in the deeper layers of the skin and along the sheaths of the peripheral nerves, just as the favorite habitat of the human variety of the tubercle bacillus is in the lungs. In the nodular or tubercular type of leprosy nodules or tubercles form in the skin. This type is analogous to the exudative or bronchopneumonic form of pulmonary tuberculosis. Bacilli are present in enormous numbers in these skin lesions and, when the nodules ulcerate, the case is comparable to the open case of pumonary tuberculosis. The mucous membrane of the nose is very commonly involved in leprosy, and the nasal secretions discharged in sneezing or in blowing the nose probably become one of the chief means of spreading the infection. From the nose the disease readily extends to the linings of the upper parts of the respiratory tract, and the bacilli are then disseminated in talking and coughing, just as in the droplet mode of dissemination of the tubercle bacillus.

In both diseases the course is commonly chronic, leprosy showing, as a rule, the greater chronicity. In the pathological course of destruction of tissue with subsequent scar-formation there is marked similarity between tuberculosis and leprosy, with the difference that in tuberculosis it is the internal organs that are most often attacked, whereas in leprosy the destructive processes are in plain view on the external surface of the body.

There is similarity in the manifestations of the tubercle bacillus and the lepra bacillus in the blood, in that there exists in both diseases a bacillaemia which is usually intermittent, and that only a few bacilli escape into the peripheral circulation and are present at any one time. In neither disease does the blood picture give clear-cut information of diagnostic or pathognomonic value. In the progress of each disease a secondary anaemia develops. In both diseases the leucocyte count may vary in the presence of complications. Weinmann (6) examined the blood in numerous different diseases for the phenomenon of nuclear inversion—predominance of polymorphonuclear neutrophiles with two segmentations over those with three—first described by Vélez and based on Arneth's formula, and found the phenomenon positive in tuberculosis, leprosy and malignant blastomata, but negative in all other diseases tested. He found this to be an early sign. The rate of sedimentation of erythrocytes bears a relation to the severity of the disease process in both tuberculosis and leprosy. Repeated estimations are, therefore, of prognostic value in both diseases. Schujman (7) recently studied the sedimentation speed in two hundred cases of leprosy in Brazil. In 8 per cent of mild cases he found the sedimentation index, representing the total sedimentation of red cells at the end of sixty minutes, normal or only slightly increased. In 80 per cent of advanced cases he found it much elevated. A persistently high index, even when the lesions were discrete, signified the approach of an acute reaction, whereas cases with persistently low index responded to treatment. These findings correspond sufficiently well with those of Kaminsky and Davidson (8) for pulmonary tuberculosis; in a series of 442 cases of pulmonary tuberculosis these investigators found the sedimentation index directly proportional to the severity of the disease. The blood chemistry, likewise, shows parallelisms in the two diseases, such as increase of the globulin fraction with advancing disease, and decrease of albumin. These are not, however, characteristic of these diseases only.

Turning to serology, Aoki and Murao (9) found the serum of lepers capable of giving strong reactions against the Witebsky-Klingenstein-Kuhn tuberculosis antigen. According to Witebsky, such reactions are antigen-antibody (specific) reactions, and the coincidence of positive reactions in these two diseases is explainable on the basis of similarity of the microörganisms and of the pathogenesis of the diseases. Taylor and Malone (10) obtained complement fixation of diagnostic importance with the sera of lepers and an antigen composed of defatted tubercle bacilli.

There is close similarity between tuberculous skin lesions and the early lesions of dermal leprosy. Wheaton and Cohn (11) saw a case of lupus vulgaris simulating leprosy not only in the skin changes of the face, hands and feet, but also in the bone changes. Where leprosy is not endemic and the pathologist is not prepared to encounter its protean histological manifestations, the differential diagnosis between nodular lesions of leprosy and tuberculosis may be delicate even with the aid of the microscope. Quérangal des Essarts and Lefrou (12) call attention to a cellular arrangement sometimes seen in the depigmented patches of leprous nodules and resembling that of the tuberculous follicle, with giant cells of Langhans type surrounded by epithelioid cells and some lymphocytes. A point of differentiation is that the nodules of leprosy are constantly vascularized.

In 1898 Jadassohn applied the term "tuberculoid" to certain eruptive skin changes observed by him in lepers, which had the essential histology of the lesion of tuberculosis. Such changes are now recognized as not uncommon. They are analogous to the tuberculids of tuberculosis and the term "leprid" is applied to them by some authors. They are closely related to the maculo-anaesthetic form of leprosy. Ordinarily, bacilli are not found in standard smears from these lesions, which is another point of similarity to the tuberculid. Wade (13) mentions that leprous lesions of this type have repeatedly been diagnosed as simple tuberculosis by competent pathologists who were simply not aware that such changes occur in leprosy. The essential histological feature is the focus of epithelioid cells, the same as in the analogous lesion of tuberculosis. Wade points out that the wandering or macrophage cell, which in cutaneous leprosy becomes the lepra cell, is the same cell which in the tuberculoid condition becomes epithelioid, and that it is not surprising that in some lesions full differentiation may not have occurred. He goes on to say that the essentially epithelioid character

of the tuberculoid lesion, entirely nonspecific and found in widely different conditions, is believed to be primarily dependent on the condition of the tissues,—a form or phase of allergy. Fialho and Ramos e Silva (14) saw a case of tuberculosis of the skin, with no lymph-node involvement, which was first diagnosed tuberculoid leprosy on the basis of hypo-aesthesia of the lesion together with the tuberculoid appearance of the histological picture. Guinea-pig inoculation proved the tuberculous nature of the disease and the lesion was successfully treated by electrocoagulation.

There are certain diseases of the skin, such as erythema nodosum, lupus erythematosus, and Boeck's sarcoid, which are believed by some students of the subject to have a more or less intimate aetiological connection with tuberculosis,—at least, for some cases. It is interesting to note that leprosy, too, seems to enter as another claimant for consideration in this somewhat confused situation. Kissmeyer and Nielsen (15), of Copenhagen, have pointed out a number of points of similarity between Boeck's sarcoid and leprosy, and state that the resemblance between leprosy and sarcoid is more marked than between tuberculosis and sarcoid. Lisi and Sebastiani (16) report a case of multiple lesions which were morphologically and structurally sarcoids and which contained acid-resistant bacilli; the future course showed leprosy. Clinical erythema nodosum, with generalized adenopathy, had been present for fifteen days in a twelve-year-old Brazilian boy seen by Ribeiro de Souza (17). The Mantoux test was negative. Guinea-pigs, inoculated with the fasting gastric juice of the patient, did not develop tuberculosis. Hansen's bacillus was discovered in the nasal secretion and in an inguinal lymph node. This boy had a brother with leprosy. He had been separated from him for eleven years. Ribeiro de Souza makes two suggestions: (1) that the erythema nodosum activated the latent leprosy by reducing immunity, in the same way that it may activate a latent tuberculosis, and (2) that the eruption, clinically erythema nodosum, was actually a leprous manifestation. Reiss (18) mentions a clinical similarity between lupus erythematosus and the early manifestations of leprosy, and believes that they may prove to be a source of diagnostic confusion in some cases.

Skin tuberculosis may coexist with leprosy. Lie (19), of Bergen, saw a case of nodular leprosy with scrofuloderma of the neck. The tuberculous nature of the enlarged cervical lymph nodes was proved by guinea-pig inoculation. Autopsy on the patient failed to reveal any

other tuberculous changes except in one bronchial lymph node. Lie states that the presence of tubercle bacilli has been verified by Oto and Sato, and points out that care must be used in attributing all tissue changes in leprotic lesions to the lepra bacillus. In Lie's case the leprous changes had receded before the tuberculous process. This agrees with what has been observed in cases in which a more generalized tuberculosis was present with leprosy.

Pulmonary tuberculosis is the most frequent complication of leprosy. Statistics differ for different localities, but it is generally stated that about 50 per cent of all deaths in leprosy are attributable to tuberculosis and that tuberculosis occurring with leprosy definitely shortens life. At the National Leprosarium at Carville (Louisiana) we have made bacterioscopic examinations of the sputum from 210 lepers for acid-fast bacilli. This work was reported by Denney (20). Forty-seven per cent of the sputa showed acid-fast bacilli, and a more intense study was then made to determine more accurately the identity of these organisms. A routine bacteriological examination of sputum from 75 of the 99 patients who had yielded sputum positive for acid-fast bacilli gave positive cultures of the tubercle bacillus from 14 cases, each of which was clinically tuberculosis. It is evident that the mere demonstration of acid-fast bacilli in the sputum of a leper does not speak conclusively for either leprosy or tuberculosis.

Does leprosy itself attack the lung? A variety of opinion exists. Muir (21) recently examined 10 cases of pulmonary disease in which leprosy of the lung could be suspected. He used the guinea-pig inoculation method in eight. In the two in which this test was omitted, the clinical course showed plainly that the disease was not tuberculosis. In one of the 8 cases tested by animal inoculation, the disease was obviously tuberculosis. In the remaining seven the inoculation gave negative results. Muir ruled out the rupture of a suppurating nodule of the larynx or pharynx in the 9 cases that were plainly not tuberculosis, and he believes that most if not all of them were definite leprosy of the lung.

SUMMARY

A similarity of leprosy to tuberculosis is shown:

1. In their causative organisms, morphologically, chemically, and tinctorially.

2. In the fact that, during intrauterine life, infection occurs rarely

if ever in either disease, though, in both, susceptibility to infection is greatest in early childhood.

3. In the constitutional and conditional factors on which frank manifestations of both diseases depend.

4. In their chronic courses, and in their febrile reactions.

5. In the manifestations of tuberculous skin lesions and some of the early lesions of dermal leprosy.

6. In the leprid and tuberculid; and in the occurrence of tuberculoid lesions in both diseases.

7. In the frequency of pulmonary tuberculosis as a complication and also as a cause of death in cases of leprosy.

8. In many of the social problems presented by both diseases.

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PROTRACTED HAEMATOGENOUS TUBERCULOSIS WITH PREDOMINANT INVOLVEMENT OF THE HEART

Report of 2 Cases[1]

SAMUEL COHEN

Although tuberculosis of the heart is considered an unusual manifestation of systemic tuberculosis, nevertheless there are many points of interest to the clinician and pathologist. In the following brief review we shall discuss the salient features of tuberculosis of the pericardium, myocardium and endocardium, particularly as part of a generalizing tuberculosis. This will be followed by a report of two cases.

INCIDENCE

Tuberculous pericarditis: According to available statistics, tuberculous pericarditis is found in about 5 per cent of all patients dying from tuberculosis and in approximately 1 per cent of those dying from all causes. As regards its relative frequency compared to other pericardial lesions, the consensus of opinion is that tuberculosis, next to rheumatic fever, is the most common cause of chronic adhesive pericarditis.

Tuberculosis of the myocardium: This is quite rare. For a long time it was considered that the heart muscle was immune to the disease. To Richard Townsend (1) of Dublin is given the credit of reporting the first case in the English literature in 1832. Valentin (2), who reviewed the literature in 1895, found in 3,203 cases of generalized tuberculosis autopsied by numerous authors only 7 with myocardial lesions (0.21 per cent). The comparative rarity of cardiac-muscle involvement was further emphasized by Norris (3), who, after a study of 7,219 necropsy protocols, noted 1,780 cases of tuberculosis, and in this group there were 82 cases of tuberculous pericarditis and only 5 instances of tuberculosis of the myocardium (0.26 per cent). Raviart (4) culled from the literature in 1906 184 cases, of which he considered only 121 to be authentic. Since then about 55 additional cases have been reported.

Myocardial tuberculosis is definitely more common in children and in

[1] From the Tuberculosis Service of Dr. B. S. Pollak, Jersey City Medical Center, Jersey City, New Jersey.

young adults. In addition, there seems to be a predominance among males in cases in which sex is mentioned.

Tuberculosis of the endocardium: There is a great divergence of opinion as to its frequency. While Weigert (5) believed that endocardial tubercles would be found in about 90 per cent of cases of miliary tuberculosis, other authors have reported a far smaller percentage. Reichenbach (6) found 8 cases in 85 autopsied children who had miliary tuberculosis. Baker (7) observed 6 instances of endocardial tuberculosis in 900 autopsies.

MANNER OF INFECTION

The heart may be involved through the following routes: Haematogenous, as part of a tuberculous bacillaemia, acute or chronic; and lymphatic extension, in which the pericardium is commonly affected from caseous mediastinal lymph nodes. Some writers believe that infection of the myocardium may come through its lymphatic vessels from these lymph nodes in the same way that it reaches the pericardium. Direct extension is almost always secondary to caseous mediastinal lymph nodes; or a caseous focus in one of the layers of the heart may invade the other structures.

PATHOLOGY

In acute generalized miliary tuberculosis the typical lesions that may affect the heart are, first, those of the pericardium. In tuberculosis of the pericardium one finds miliary tubercles in varying numbers accompanied by very little exudation. When the process is of lymphatic origin, these tubercles are most numerous in the parietal layer; in haematogenous involvement, the epicardium is the most common site. Acute tuberculous pericarditis is of greater clinical importance and is characterized by fibrinous, serofibrinous and haemorrhagic exudation with some tubercle-formation.

At this point, we wish to digress and refer to the term, *primary tuberculous pericarditis*, which has appeared again in the recent literature through the writings of Hedblom (8), Riesman (9), Rawles (10), Thompson (11), Bellett, *et al.* (12). This form is subdivided into clinically and anatomically "primary" cases. In the former group are included instances of pericarditis without pulmonary tuberculosis, even though there is present caseous mediastinal adenopathy. The term, *anatomically primary pericarditis*, connotes that the pericardium alone at

autopsy is the seat of tuberculous disease. With our present status of knowledge it is difficult to visualize "primary" pericardial tuberculosis as a distinct pathological entity. We agree with Wells (13) that the pericardium, being a closed internal serous sac, must receive tubercle bacilli from some other source. In many of these reported cases, the pathological study left much to be desired. For clarity of thinking we believe that the term, *primary tuberculous pericarditis*, should be discarded.

In tuberculosis of the myocardium millet-seed-sized tubercles may occur. There is a marked discrepancy in the literature as to its relative incidence. Thus Weigert (5) believed that miliary tubercles in the myocardium were found very frequently in acute generalized miliary tuberculosis. Simmonds (14), however, did not find a single case of miliary tubercles in the heart of 126 autopsies on children. Horn (15) observed three cases in 34 patients who had acute haematogenous tuberculosis. Grethmann (16), who has had a very extensive experience with various forms of haematogenous tuberculosis at Bellevue Hospital, is in accord with Weigert's opinion. He believes that miliary myocardial tubercles are almost always present in these cases, although not as numerous as in other organs, like the lungs, spleen, kidney. They are overlooked because it is difficult, if not impossible, to observe these lesions macroscopically, due to the slight color contrast, and an attempt to detect them microscopically in a single tissue section is a very inadequate procedure. Serial sections from various parts of the heart would reveal, according to Grethmann, a greater incidence of miliary tubercles in the cardiac muscle than is reported by most writers.

In the endocardium, morphologically, we again may find miliary tubercles in the acute case of haematogenous tuberculosis. As for the sites of the lesions, Baker (7) found in 13,000 autopsy protocols from the Johns Hopkins Hospital that the following were the most frequent areas for localization of endocardial tubercles: "the right ventricular endocardium beneath the pulmonary valves; the papillary muscles; and the base of the valve (most often in the case of the mitral valve, rarely in the aortic)."

In chronic protracted lymphohaematogenous tuberculosis the predominant lesions that may occur in the heart are as follows:

1: Pericardium: The serous sac may show thickening and synechiae of its layers, tubercle-formation and caseation in various proportions. Tuberculous pericarditis may heal by resorption or organization of the exudate, resulting usually in the formation of adhesions. In caseous lesions, calcification will occur.

In chronic adhesive tuberculous pericarditis, the heart is frequently enlarged. One often sees an associated chronic mediastinitis with venous obstruction producing Pick's syndrome.

2: Myocardium: Grossly, the lesions appear in these readily distinguishable forms: the nodular type or confluent tubercles; and the diffuse caseous infiltrative type. This is the rarest of myocardial involvement. Only 12 cases had been collected by Raviart (4) up to 1906. The heart is almost always enlarged and there is usually an associated pericarditis. Microscopically, there are areas of caseation and tuberculous granulation tissue, with lymphocytes, plasma cells, and giant cells of the Langhans type. The muscle fibres show fragmentation, loss of striation, nuclear changes and vacuolization to varying degrees.

Considering the site of the lesions, apparently any part of the cardiac musculature may be affected, but certain areas are more commonly involved than others. Valentin (2) believed that the ventricles were the favorite sites, and in his collected series found no mention of auricular involvement. According to Anders (17), smaller nodules are usually present in the ventricles and the large tubercles generally in the auricles. The occurrence of the lesions in the right auricle suggests the possibility of direct extension from caseous bronchopulmonary lymph nodes, because of the close proximity of these two structures.

Another variety of involvement of the myocardium has been referred to as a tuberculous interstitial myocarditis,—a diffuse sclerosis of the heart muscle. This was first described by Brehmer (18) in 1883. However, there is no convincing evidence to support this as a pathological entity.

As regards tuberculous lesions in the blood-vessels of the myocardium, Gouley, *et al.* (19) have again called our attention to three types of changes in the coronary vessels: "intimal tubercle-formation; thickening of the intima, which may produce occlusion due to inflammatory changes in the subintimal layer; and tuberculous invasion of the adventitia."

3: Endocardium: The lesions may present themselves mainly as large nodules or conglomerate tubercles, or as caseous endocardial masses.

As in the case of the myocardium, some authors have reported instances of a tuberculous endocarditis,—a diffuse sclerosis involving the valvular endocardium, due mostly to toxins. Again, others disagree as to the validity of the pathological evidence for this entity.

It may not be amiss at this point to refer briefly to tuberculosis of the great vessels of the heart. These vessels may be involved by direct extension from a tuberculous lesion outside of the vessel which is almost

always a caseous lymph node. This is more likely to occur in cases of protracted dissemination. Resultant compression phenomena may manifest themselves, such as a distention of veins in the thorax, neck, swelling of the face, oedema of extremities, etc. Or, the vessels may be involved by direct implantation of tubercle bacilli from the blood-stream, producing intimal tubercles. This happens most frequently in cases of acute generalized miliary tuberculosis.

In presenting the pathological features in the above manner, we do not wish to convey the impression that the cardiac lesions occurring in these two forms of haematogenous tuberculosis are necessarily exclusive of each other. Thus, in the protracted type, miliary tubercles in the heart may often be present, just as in the spleen, lungs, etc. Our purpose has been simply to visualize the particular pattern of systemic tuberculosis as determining the more predominant lesions that may involve the heart.

DIAGNOSIS OF TUBERCULOSIS OF THE HEART

A tuberculous affection of the pericardium may be present without any clinical symptoms or signs whatsoever. In these cases, the pericardial lesion is usually a postmortem discovery. In other cases, there are the clinical findings of either an acute or chronic adhesive pericarditis. The symptoms and signs in this group are the same as in any acute or chronic inflammation of the pericardium, regardless of aetiology. A presumptive diagnosis of tuberculous pericarditis is justifiable in the presence of tuberculosis elsewhere. A diagnostic paracentesis is advocated when fluid is suspected, and the fluid should be studied cytologically, bacteriologically and by animal inoculation.

The diagnosis of myocardial tuberculosis is difficult and is rarely made. Patients with functional or organic heart disease will exhibit symptoms and signs in no way different from cases with tuberculosis of the heart muscle. While there is nothing characteristic one should be alert to the possibility of myocardial involvement in patients with lymphohaematogenous tuberculosis, when there is evidence of tuberculous pericarditis and abnormal cardiac rhythm. Ectopic rhythm was noted in 50 per cent of Gouley's (19) cases (auricular fibrillation in two instances and auricular extrasystoles in one case).

The diagnosis of endocardial tuberculosis is almost always made at autopsy. Clinical findings are not distinctive and a presumptive diagnosis may be entertained in a case of generalizing tuberculosis in which symptoms and signs point to involvement of the heart.

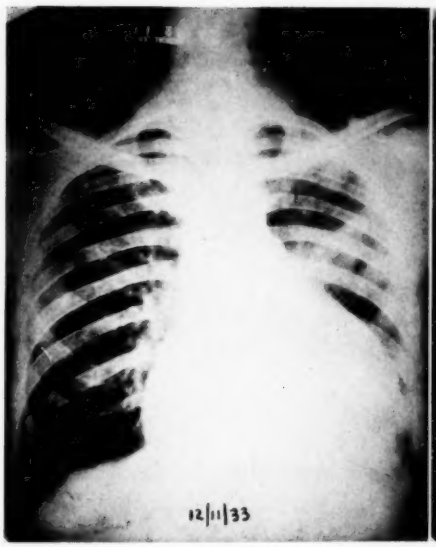
CASES

1: R. F., a thirty-year-old Negro male was admitted to the Surgical Service, November 21, 1933. His chief complaints were cough of three weeks' duration, rectal tenesmus, and haemorrhoids. The only significant points in the past history were a gonorrhoeal infection in 1926 and the story of twelve intravenous injections. Thrombosed external haemorrhoids were removed under local anaesthesia November 22. On December 7, 1934, the heart was found to be markedly enlarged to the left and the heart-sounds distant. An X-ray of the chest (figure 1), taken four days later, showed evidence of a massive pericardial effusion, together with a triangularly shaped area of density extending outward from the left hilum below the 3rd anterior rib. Light mottling was noted along the inner and midzones of the 1st, 2nd and 4th interspaces on the left side. Similar mottling was present in the 2nd and 3rd right interspaces. Both costophrenic angles were clear.

Pulmonary tuberculosis was suspected. Three sputum examinations, done during December, however, were negative for tubercle bacilli. Blood serological tests were negative. Urethral and prostatic smears were negative for gonococci.

Subsequent chest roentgenograms taken at approximately monthly intervals showed a decrease in the size of the cardiac silhouette, with resorption of the pericardial effusion (figure 2), which, incidentally, was never aspirated. The density radiating from the left hilum increased in size, and there also appeared a widening of the upper mediastinum. Both of these areas were believed to represent the seats of caseous lymph nodes. Increasing infiltration was observed in the left lung field and to a lesser extent on the right. A small effusion was first noted in the right pleural cavity in January, 1934. A similar effusion appeared in the left pleural cavity in March, 1934. Straw-colored fluid, which showed a predominance of lymphocytes was aspirated on several occasions. The patient continued to have a cough, with about one ounce of mucopurulent sputum daily, but no haemoptysis. Fever ranged on the average between 99° and 102°. On August 6, 1934, the patient was transferred to the Tuberculosis Service. Physical examination disclosed a chronically ill-appearing and somewhat dyspnoeic patient. *Chest: right lung:* Dulness in lower two-thirds of the axilla and posteriorly from the 7th vertebral spine to the base, with diminished breath-sounds. *Left lung:* Marked dulness from apex to 5th anterior rib and posteriorly from apex to 4th vertebral spine, with diminished breath-sounds, and coarse râles to 3rd anterior rib; similar râles in upper third of axilla, dulness in lower two-thirds of axilla and diminished to absent breath-sounds at the base. (Now the concentrated sputum test was positive for tubercle bacilli which was later confirmed by guinea-pig inoculation.) *Heart:* The apex beat was not seen or felt. No pericardial bulging or systolic retraction of the interspaces was noted. The cardiac borders were

Fig. 1



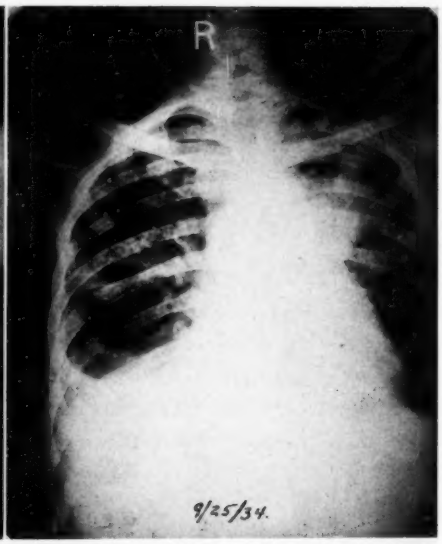
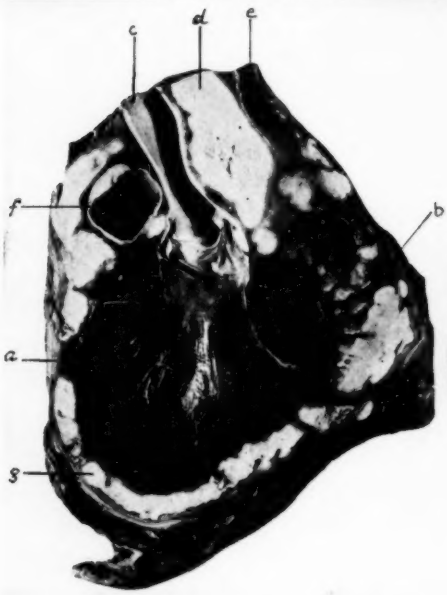


Fig. 2

Fig. 3



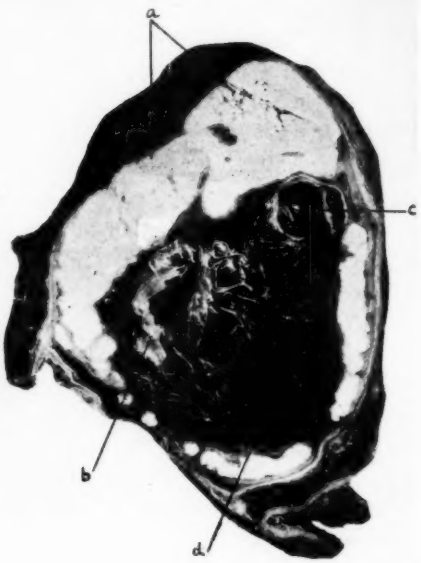


Fig. 4

Fig. 1. Pericardial effusion; left hilar density; infiltration in left lung and less in right lung

Fig. 2. Enlarged heart; increased left hilar density; annular shadows to third left anterior rib; widening of upper mediastinum (right); right pleural effusion

Fig. 3. a, left ventricle; b, caseous nodules in right auricle; c, narrowed ascending aorta; d, caseous lymph node; e, narrowed superior vena cava; f, pulmonary artery invaded by caseous lymph node; g, caseation between two pericardial layers

Fig. 4. a, massive caseous infiltration of right ventricular wall; b, tricuspid valve; c, pulmonary vessel orifice; d, thickened epicardium

difficult to map out because of the overlying pulmonary dulness. The heart-sounds were distant, rapid and regular, and no murmurs were heard. The second aortic sound was slightly louder than the second pulmonic. The blood-pressure now was 122/76 as compared with 118/66 on admission in November, 1933. An electrocardiogram, taken September, 1934, showed inversion of the T wave in all three leads. During the second week in October, gallop rhythm was noted. *Abdomen:* The liver was smooth and firm, and its edge felt 8 cm. below the costal margin. The left lobe was also enlarged. The spleen was palpable just below the costal margin. No shifting dulness present. *Extremities:* In February, 1934, the patient complained of swelling and slight pain in the left knee joint. Examination in August revealed a fusiform, painless, cold swelling of this joint with slight limitation of motion. Straw-colored fluid, varying in amount from 20 to 50 cc., was aspirated on three occasions. The smear showed lymphocytes and polymorphonuclear cells, with a predominance of the latter. Smear was negative for tubercle bacilli, culture sterile, and guinea pig inoculated with fluid died one month after injection and no evidence of tuberculosis was found. The complement-fixation test for gonorrhoea was done on this fluid and also reported negative. X-rays showed atrophic changes in the left knee joint. In May, 1934, the patient's attention was called to swelling of his left wrist. In August there was noted moderate swelling of the wrist but no redness or pain,—carpus apparently solid,—the right wrist was also stiff,—carpal bones solid. X-rays of the wrists showed disintegration of the carpal bones with loss of the normal interarticular lines. In July, there developed a painless swelling of the left foot just distal to the internal malleolus. There was a slight pain on lateral movement of the joint. X-ray of the tarsal bones in September, 1934, showed considerable decalcification of the bones, with narrowing of the articulating surfaces. An X-ray of the right ankle revealed a rarefied area within the medullary portion of the lower third of the right tibia and about 1½ inches in diameter, indicating a destructive process within the bone. A search for superficial lymph nodes revealed one, the size of a lima bean, in the neck, while a few axillary and bilateral inguinal nodes were enlarged and of firm consistency.

In September, 1934, the patient developed evidence of myocardial insufficiency, with marked ascites and bilateral pretibial oedema extending up to the knees. In October the face was swollen and there was pitting oedema of the wrists and forearms. The patient was placed on digitalis and salyrgan therapy. In three weeks there was a marked recession of the oedema, with loss of 25 lbs. The patient became increasingly weaker and expired October 22, 1934, eleven months after admission to the hospital.

The final clinical diagnosis was protracted haematogenous tuberculosis, with chronic pulmonary tuberculosis; tuberculous lymphadenitis; tuberculous polyserositis, with adhesive pericarditis and myocardial insufficiency; and tuberculous polyarthritis (Poncet type).

Postmortem Examination

The autopsy was performed twenty hours after death on an embalmed body. *Thoracic cavity:* The right pleural cavity contained about 300 cc. of dark red fluid, and the left pleural cavity 200 cc. of the same kind of fluid (color due to embalming solution most likely). Both lungs were adherent posteriorly over the apices, and there were also broad dense adhesions to the pericardium and to both diaphragmatic leaflets. The anterior and superior mediastinal space was widened, and occupied by masses of enlarged and caseous bronchopulmonary, tracheobronchial and paratracheal lymph nodes. *Lungs: right:* The pleura was rough and dull, and slightly discolored by the dark red embalming fluid; there were broad adhesions between the upper, middle and lower lobes. On section were revealed several small confluent cavities lined by a thin yellowish caseous abscess-membrane in the upper lobe. Scattered throughout the remainder of the entire lung were clover-leaf-like and rosette-like yellowish patches of caseation, together with caseous casts of the smaller bronchi. In addition, numerous miliary and slightly larger nodules were noted. *Left lung:* The outer aspect was the same as described for the right lung. Broad adhesions were present between the upper and lower lobes. On section were seen several enlarged, caseous bronchopulmonary lymph nodes encroaching upon the parenchyma of the lung. The upper lobe contained several moth-eaten areas of excavation, whose walls were lined by a yellowish abscess-membrane. Surrounding these cavities and in scattered areas of the lower lobes were yellowish patches of caseation of sublobular and lobular size. There were numerous miliary and conglomerate miliary nodules disseminated over both lobes. *Heart:* The heart was very much enlarged and weighed 1,025 gm. The largest posteroanterior circumference was 45 cm., and maximum length 16.2 cm. The pericardium was very thickened and roughened by fibrinous tags,—no nodules noted. The great vessels of the heart (the pulmonary artery with its two branches, the aorta and superior vena cava), and right and left main bronchi were completely surrounded by masses of caseous lymph nodes, which seemed to extend into the pericardium and myocardium. Some of these nodes surrounding the bronchi were anthracotic with several caseous foci. *Right auricle* (figure 3): The right auricular wall was replaced in part by many irregular nodular areas of caseation, which seemed to be continuous with caseous paraäortic lymph nodes. The nodules varied from 1 to 2 cm. in diameter. *Right ventricle* (figure 4): The thickness of its wall varied from 1.0 cm. on its diaphragmatic surface to a maximum of 4.0 cm. on its right lateral wall. On this latter aspect, the actual myocardium attained a thickness of but 0.6 cm., the remainder being replaced by massive caseous material. Along the anterior facies of the ventricle was a band of caseation about 1.0 cm. in diameter imbedded between the two thickened layers of pericardium. The

muscle on the diaphragmatic surface showed strands of fibrosis and slight invasion by caseation. The endocardial lining was smooth and glistening. The pulmonary and tricuspid orifices were normal. The leaflets were soft, pliable, translucent. The papillary muscles and *chordae tendinae* were normal. *Left auricle:* The endocardium and myocardium were normal. Between the pulmonary artery and the auricular wall were large caseous peribronchial nodes. A portion of the artery was definitely invaded by caseous material. *Left ventricle* (figure 3): Along its surfaces was a slightly irregular zone of caseation (1.0 cm. in diameter), bounded internally for the most part by thickened epicardium. The endocardial lining was smooth and shining. The leaflets of the mitral and aortic valves were thin and translucent, and had free edges. The *chordae tendinae* were slender and the papillary muscles normal. The coronary arteries were patent and had elastic walls. One centimetre above the base of the aortic valve, the ascending aorta was constricted by surrounding large caseous paraäortic nodes. The same lymph nodes also compressed the superior vena cava. The inferior vena cava, however, was normal. *Abdominal cavity:* The peritoneal cavity contained about 200 cc. of dark red fluid (color due to embalming solution). The omentum and the serosa of the intestines were studded with numerous grayish-white nodules of millet-seed size and slightly larger. The mesenteric and retroperitoneal lymph nodes were very much enlarged and caseous. *Spleen:* Slightly enlarged. Scattered all over the cut-surfaces were numerous yellowish and caseous lesions, measuring from 1.0 mm. to 1.5 cm. in diameter. *Liver:* Greatly enlarged and firm. Under the capsule and in the parenchyma on cut-section were several yellowish caseous foci, varying from 1.0 mm. to 2.0 cm. in diameter. *Kidneys:* Both were enlarged. The left showed a caseous nodule, measuring 1.0 × 3.0 cm. in the upper pole of the cortex. The lesion extended about 3.0 cm. into the medulla.

Microscopic examination: Lungs: Sections through the right and left upper lobes showed a predominantly productive tuberculous process, with numerous giant cells, collections of lymphocytes and fibrous tissue. Few caseous foci were present. *Heart: section through left ventricle* (figure 5): Pericardium very thickened, vascular, and composed of dense hyaline fibrous tissue with some lymphocytes, plasma cells, and fibroblasts. Large caseous areas present and delimited by thickened epicardium. In some areas the myocardium revealed caseous tuberculosis with swelling of the fibres, loss of striation, vacuolization, and lymphocytic infiltration. Other microscopic fields showed poorly stained seminecrotic masses of fibrils. A smear of this material was positive for tubercle bacilli. *Section through right auricle* (figure 6): Poorly stained conglomerate mass of caseous tuberculosis, with a narrow rim of lymphocytes, epithelioid cells, and polymorphonuclear leucocytes. The muscle fibres showed actual destruction by the tuberculous invasion, with fragmentation,

Fig. 5

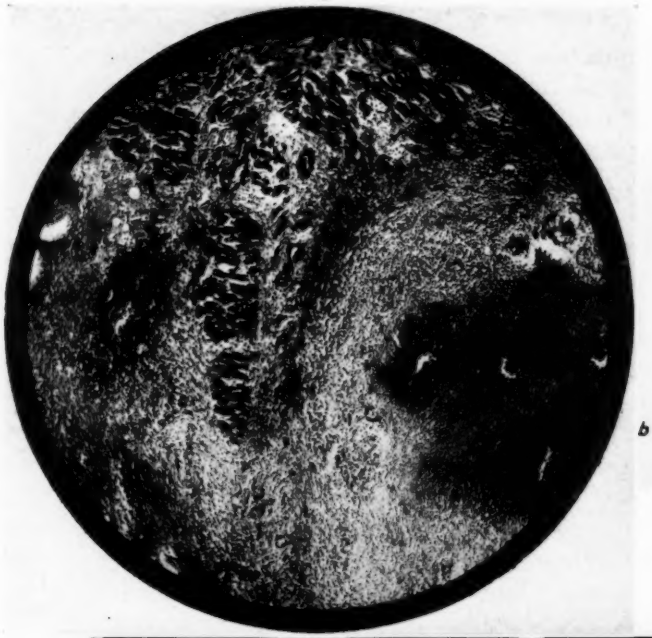


Fig. 6

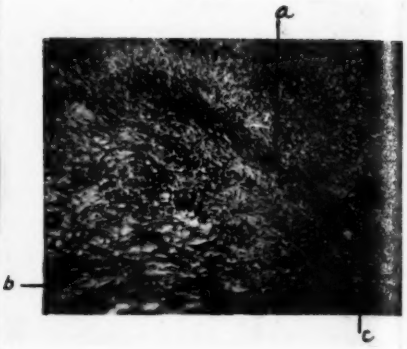


Fig. 7

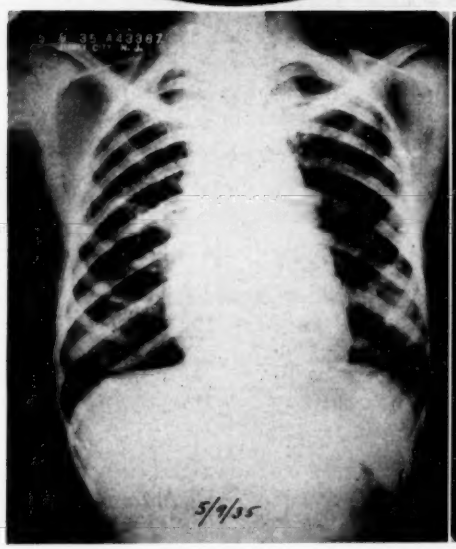


Fig. 8

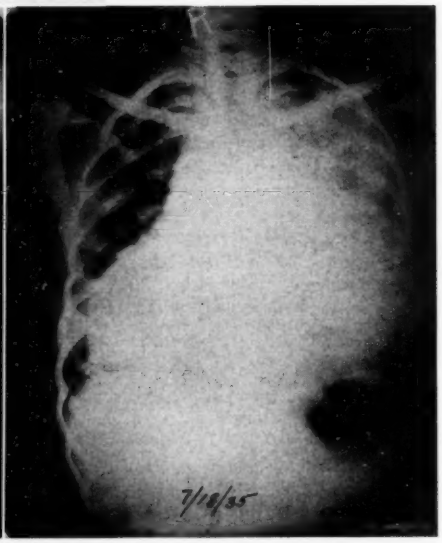


Fig. 5. Section through muscle layer of left ventricle, showing tuberculous invasion

Fig. 6. Section right auricle (×50 diameter): a, caseation in muscle layer; b, swollen fragmented fibres; c, invasion of endocardium

Fig. 7. Disseminated light infiltration, both lungs, with small honeycombed areas in apices; widening of upper mediastinum; increased transverse diameter of heart

Fig. 8. Increased infiltration (right); dense confluent bronchopneumonic areas (left), with areas of "high light" above 5th rib; further increase in width of cardiac shadow

loss of striation, and vacuolization. One of these conglomerate caseous masses reached the endocardial surface. *Section through pulmonary artery:* The artery was surrounded by a conglomerate mass of caseation, with a peripheral zone of lymphocytes, epithelioid cells and little fibrous tissue. The adventitia, which was partly invaded, showed areas of perivascular leucocytic infiltration. At one point there was invasion of the *tunica media*, with destruction of elastic and muscle fibres and extension into the intimal layer.

Final anatomical diagnosis: Caseous tuberculous lymphadenitis of bronchopulmonary, tracheobronchial, paratracheal, paraäortic and superior mediastinal lymph nodes, with compression of superior vena cava, portion of ascending aorta and invasion of left pulmonary artery; similar involvement of mesenteric and retroperitoneal lymph nodes; protracted haematogenous tuberculosis (small to large nodules), with involvement of lungs, liver, spleen, kidneys, omentum, and serosa of intestine; chronic ulcerative tuberculosis of both upper lobes with bronchogenic dissemination into the dependent parts of both lungs; tuberculous pleuritis, mediastinitis, perihepatitis; caseous tuberculosis of pericardium and myocardium, with extension into endocardium.

Interpretation of pathological findings: The main points to be considered are (1) the pathogenesis of the case; (2) an explanation and correlation of the numerous, multiform lesions in various and remote organs; and (3) the involvement of the heart.

It must be apparent that, for the variety in the form and size of the lesions present in numerous organs, this case falls into the group of protracted haematogenous multiform tuberculosis. This type, seen most frequently in the colored race, has been repeatedly emphasized in recent years as a distinct clinical and pathological entity by Grethmann (16). The characteristic findings in these cases are panadenitis and panserositis. The spleen is the best indicator at the autopsy table of a protracted tuberculosis.

Judging from the extensive bronchopulmonary lymph-node involvement at the left hilum, the left lung was most likely the site of the first parenchymal tuberculous infection. From the primary focus in this lung, the infection spread to the above mentioned regional lymph nodes, and then to the tracheobronchial and paratracheal nodes, resulting in a progressive caseous tuberculous lymphadenitis of the mediastinal lymph nodes. The stage was then set for invasion of the circulatory system *via* the "venous angle", namely, the thoracic duct, internal jugular vein, and right heart, with dissemination into the lungs and other organs of the body. If we now assume that this invasion occurred at repeated intervals with various dosages of bacilli and toxins, we can readily account for the variations in form and size of the resulting lesions. In like manner, we can explain the involvement of distant groups of lymph nodes as well as of the serous membranes. The latter react with serofibrinous exudation to this protracted dissemination.

The lesions in the lungs were of interest. They were of two kinds: round foci of different size, with no relation to the bronchial tree (haematogenous origin) and cavities and rosette-like or clover-leaf-like lesions. These cavities most likely had their origin from metastatic haematogenous foci, which ruptured into the bronchi or bronchioles and gave rise subsequently to typical bronchogenic dissemination. (As noted, there was direct invasion of the coats of the pulmonary artery. The possibility of spread of tubercle bacilli from the lesion in this vessel into the lung beds must certainly be considered.)

With regard to the heart, it is important to recall that the greatest involvement occurred in the pericardium and myocardium. In view of the extensive tuberculous lymphadenitis affecting the lymphatic systems at the base of the heart, we are of the belief that the unusual caseous involvement of the cardiac chambers was due to a direct extension from these caseous mediastinal lymph nodes into the pericardium and myocardium. Involvement of the pericardium was most likely primary, with secondary myocardial and endocardial extension. The above is probably the simplest explanation of the pathological picture.

Comment on clinical findings: The case presented the clinical criteria of protracted haematogenous tuberculosis. Myocardial tuberculosis was not suspected, and the signs of cardiac decompensation were attributed primarily to a chronic tuberculous adhesive pericarditis. In retrospect, the evidence of gallop rhythm plus the existing pericarditis should have been a sufficient clue to make us suspect possible involvement of the other structures of the heart.

Swelling of the neck, face and portions of the upper extremities were probably manifestations, in part at least, of compression of the superior vena cava.

Another interesting aspect of this patient's clinical course were the symptoms and signs referable to the joints. Development of the joint symptoms during the dissemination of tubercle bacilli to other parts of the body, the insidious onset, cold swelling of the joints, X-ray evidence of destruction of the carpal and tarsal bones and the right tibia, with loss of the normal interarticular lines, seemed to indicate a tuberculous polyarthritis (Poncet type). Unfortunately, a final diagnosis was not possible as the joints were not opened at autopsy.

2: B. B., a twenty-four-year-old married colored female was admitted to the Medical Service, June 27, 1935, and transferred to the Tuberculosis Service, July 11, 1935. Her chief complaints were cough since April, 1935, with expectoration of 1 to 2 ounces of mucopurulent sputum; dyspnoea on mild exertion; and anorexia, with loss of 31 lbs. since January, 1935. There was nothing significant in the past history.

Physical examination on admission showed a chronically ill-appearing dyspnoeic patient. *Right lung:* Dulness from apex to 2nd rib anteriorly, throughout axilla and posteriorly over upper lobe; crackling râles in lower third of axilla. *Left lung:* Dulness throughout, with areas of *B.B.* and *B.V.B.* anteriorly and in axilla, with numerous coarse crackling râles throughout posteriorly. *Heart:* Apex beat not visible; no shock or thrill felt; sounds of greatest intensity in 2nd interspace, one inch to right of the midsternal line; first sound of fair myocardial quality and regular; no murmurs. B.P.: 100/70. *Abdomen:* No evidence of ascites; spleen and liver not felt. Bilateral cervical and epithrochlear lymph nodes were palpable. A concentrated sputum specimen was positive for tubercle bacilli. Wassermann negative.

Chest X-ray of July 18, 1935 (figure 8) showed disseminated infiltration throughout the right lung, with a few honeycombed areas in the 1st and 2nd interspaces and a dense bronchopneumonic shadow (left) containing several areas of "high light." There were a widening of the upper mediastinum and an increase in the transverse diameter of the heart much more to the right. A diagnosis of pulmonary tuberculosis, mediastinal adenitis and possible dextrocardia was made. However, we were fortunate in obtaining shortly afterward an X-ray taken on May 9, 1935 (figure 7), when she was attending the out-patient clinic. Now, it seemed apparent that the impression of a dextrocardia was erroneous, and that what had most likely happened was a rupture of one or more caseous bronchopulmonary nodes into a bronchus, giving rise to an extensive confluent tuberculous bronchopneumonia: also, serofibrinous pericarditis was suspected, but there was no attempt at aspiration of fluid.

On August 2, 1935, a definite pleuropericardial friction rub was heard, which persisted until the latter part of September. No endocardial murmurs were heard. A hypotension persisted, and the last recorded blood-pressure reading, five days before death, was 88/64. An electrocardiogram (July 26, 1935) showed regular sinus rhythm with erect T waves in all three leads. The last one, taken September 29, 1935, revealed low voltage with flattened T waves, and regular sinus rhythm was maintained. However, on October 17 some extrasystoles were present and prevailed until death. Fluoroscopy on several occasions showed somewhat feeble cardiac pulsations. Dependent oedema was never noted. In October, the liver was felt just below the costal margin. The spleen was not enlarged. The patient became slightly more dyspnoeic, weaker and emaciated, and several days before exitus she became drowsy. There were no signs of meningeal irritation, and examination of the spinal fluid was normal. The patient died October 28, 1935.

The final clinical diagnosis was protracted haematogenous tuberculosis with chronic pulmonary tuberculosis; tuberculous lymphadenitis; and tuberculous pericarditis with probable tuberculosis of myocardium.

Postmortem Examination

The autopsy was performed several hours after death. *Thoracic cavity:* No fluid was found in either pleural cavity. Both lungs (more so the left) were densely adherent to the chest-wall, diaphragm and pericardium. In the mediastinum was a large matted group of caseous bronchopulmonary, tracheobronchial and paratracheal lymph nodes encroaching upon the great vessels of the heart. On freeing the thoracic contents, a large yellowish caseous mass, measuring about 5.0 cm. in diameter, was in juxtaposition to and invaded the 9th and 10th dorsal vertebrae. The heart and lungs were removed *in toto* and several longitudinal sections were made. *Lungs: Right:* The parietal pleura was dull and thickened. Several small yellowish nodules were noted on the visceral layer. The oblique and horizontal fissures were obliterated by adhesions. On section, there were a few moth-eaten necrotic areas in the posterior portion of the upper lobe. Some of the small cavities, measuring 0.5 to 1.0 cm. in diameter, had a thin yellowish caseous lining-membrane. Throughout the lung, but more marked in the upper lobe and posterior portion of the lower lobe, were numerous small round whitish lesions, most of which measured 1.0 cm. in diameter. There were a few yellow patches of sublobular size. Scattered anthracotic foci were noticed. At one point in the wall of the right main bronchus, 3.0 cm. (figure 9) from the bifurcation of the trachea, was an opening, 3.0 × 5.0 mm. in diameter, which led into a caseous bronchopulmonary lymph node. *Left lung:* The parietal pleura was dull and thickened, showing several yellowish small caseous foci, particularly over the anterolateral surface. A small effusion was present in the oblique fissure and in the mediastinal pleura. Serial sections of the lung revealed an irregularly-shaped cavity, 1.0 × 3.0 cm. in diameter, in the apex posteriorly just beneath the thickened pleura. There were several small scattered moth-eaten cavities lined by caesous membranes, together with numerous yellow patches of lobular and sublobular size, clover leaf lesions and caseous casts of smaller bronchi, between which were interspersed anthracotic areas. Some lesions were round, white in color, and measured 1 to 2 mm. in diameter. The left main bronchus was surrounded and narrowed by many caseous lymph nodes (some containing anthracotic foci). Some of these nodes encroached on the parenchyma, but no point of rupture into the bronchus was noted. In the inferior medial portion of the lower lobe was a fine "honeycomb" appearance, and an emphysematous bleb was noted at the extreme lateral portion of the lower lobe. *Heart:* The organ was enlarged, and its greatest transverse diameter was 12.0 cm. The parietal pericardium was hyalinized, and measured 1 to 2 mm. in thickness. Visceral and parietal layers were adherent. No nodules noted. There were a few small caseous lymph nodes at the base of the heart.

Serial longitudinal sections revealed the following: *Right auricle* (figure 10): The endocardium was smooth and glistening; 1.5 cm. below the entrance of

Fig. 9

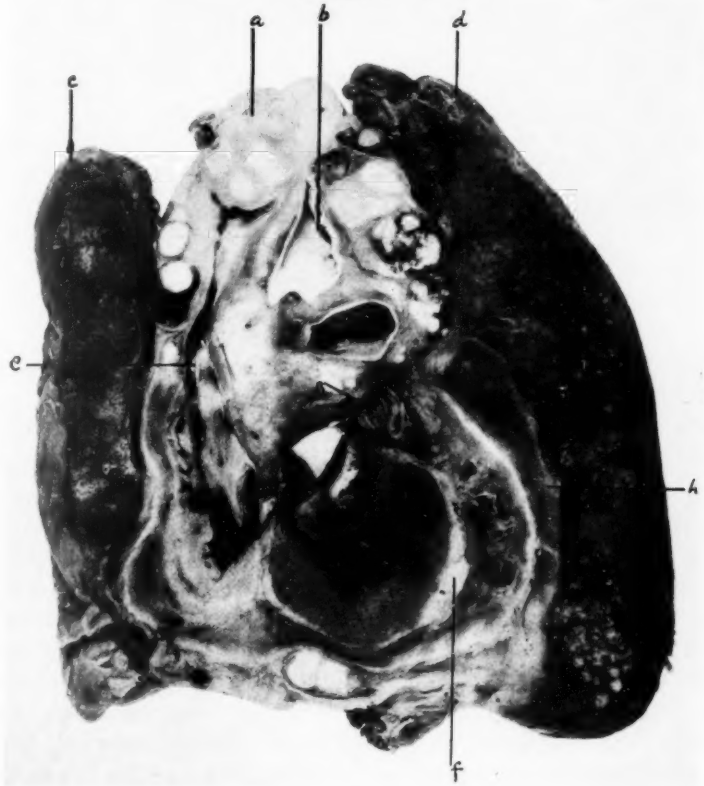


Fig. 10

Fig. 9. Arrow indicates rupture of caseous lymph node into right main bronchus

Fig. 10. a, mass of caseous mediastinal lymph node; b, aorta invaded by caseous lymph node; c, right lung; d, left lung; e, caseous nodule in right auricle; f, caseous lesion; g, left auricle; h, "fixed fluid" in mediastinal pleura

the superior vena cava was a yellowish caseous nodule, 1.5 × 0.8 cm. in diameter, embedded in the auricular wall. The reverse side of the section showed this to be a caseous anthracotic bronchopulmonary node which had apparently invaded the auricle. The epicardium was very thickened and showed a caseous focus. *Right ventricle:* Its right lateral wall measured 7.0 mm. The epicardium here was very thickened, showing a narrow zone of haemorrhage and a small band of caseous material, 1 to 2 mm. in width and 2.0 cm. in length, which extended into the muscle. *Left auricle* (figure 10): The endocardium and myocardium were normal. *Left ventricle* (figure 10): The muscular wall varied in thickness from 1.0 to 2.0 cm. Epicardium very thickened (portion inadequately fixed). Several small irregular caseous foci in right, extending into the muscle. Endocardium smooth and glistening. The papillary muscles and leaflets of the mitral valve were normal. One section showed a caseous lymph node extending into the lumen of the aorta (figure 10). There was no visible point of rupture and the intimal lining was smooth. *Abdominal cavity:* No fluid in the peritoneal cavity. The lower anterior edge of the liver extended one inch below the costal margin. No evidence of tubercles on the omentum, serous surface of intestines or parietal peritoneum. The mesenteric and retroperitoneal lymph nodes were enlarged and caseous. *Spleen:* Not enlarged: section showed innumerable small whitish lesions, measuring 0.5 to 2.0 mm. in diameter throughout the splenic pulp. Some of these lesions coalesced. *Liver:* Enlarged and firm. Capsule was thickened on the superior surface and adherent to the right diaphragm. Shining through the capsule were a few small grayish-white foci, about 2.0 mm. in diameter. Section showed normal lobular markings. *Kidneys:* The right kidney was enlarged. In the superior pole of the cortex was a small yellowish-white focus, 1.6 mm. in diameter. The left kidney was small, and the capsule stripped readily, presenting several small pinhead yellowish-white lesions. *Gastrointestinal tract:* Several small punched-out ulcers were present at the ileocaecal junction.

Microscopic examination: Lungs: section through right upper lobe: Numerous interstitial tubercles of varying size and age. Compression of some alveoli, while others were emphysematous. Considerable vascular engorgement, with pigment-laden phagocytes in the lumina. Scattered areas of mononuclear leucocytes. Pleura thickened with subpleural anthracotic deposits. *Section through apex of left lung:* Diffuse fibrocaseous tubercles of varying size and age (the majority were extremely large and caseous). Little recognizable parenchyma remained. The alveoli were filled with oedema fluid and groups of alveoli were emphysematous. Pleura markedly thickened. *Heart: section through pericardium and left ventricle:* Pericardium very thickened, and composed of a dense hyalin fibrous tissue with few cellular elements. At several points, the fibrous tissue was delimited by tuberculous areas of varying size;

the largest showed extensive caseation; muscle fibres were invaded in some areas, and showed fragmentation, loss of striation, and lymphocytic infiltration. Endocardium thickened. *Section through caseous focus in right auricle* (figure 11): Muscle fibres swollen, and hazy, with loss of striations. Opposite the areas of greatest caseation the muscle layer was thinned and almost completely gone. (Calcification present in the centre of some of the caseous areas.) Endocardium considerably thickened but not invaded by the tuberculous process.

Final anatomical diagnosis: Caseous tuberculous adenitis of bronchopulmonary, tracheobronchial, paratracheal, paraäortic, superior and posterior medi-

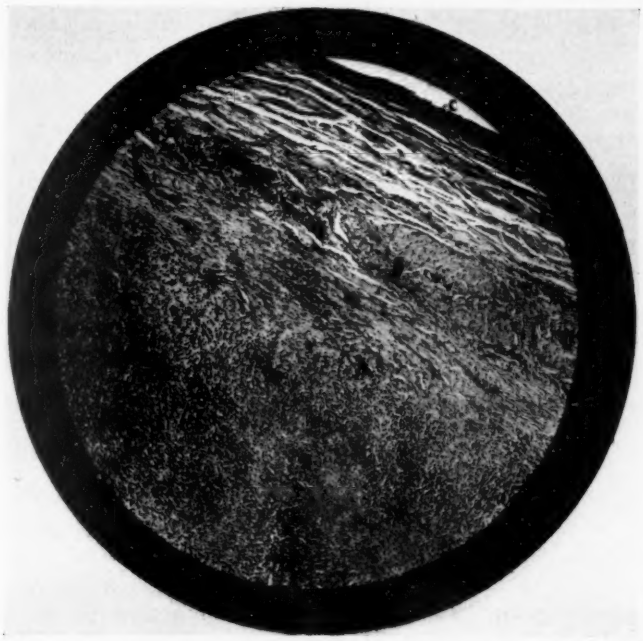


Fig. 11. Section right auricle (×50 diameter): a, necrosis and caseation; b, swollen muscle fibres; c, thickened endocardium

astinal lymph nodes with erosion into the right main bronchus, dorsal vertebrae (IX and X); and encroachment upon the lung parenchyma and ascending aorta. Caseous tuberculous involvement of mesenteric and retroperitoneal lymph nodes; haematogenous tuberculosis (small nodules) of lungs, liver, spleen and kidneys; chronic ulcerative tuberculosis of both lungs, most marked in the left upper lobe, with widespread bronchogenic dissemination in the left lung; tuberculous pleuritis and mediastinitis; fibrocaseous tuberculosis of pericardium and myocardium; chronic ulcerative tuberculosis of the intestines.

Interpretation of pathological findings: This case is less outstanding than the

previous one as a representative of the group of protracted haematogenous tuberculosis. While caseous lymphadenitis was marked, the features of multiform lesions and serous effusions were less prominent. The mode of systemic dissemination, however, must have occurred in a similar manner although the dosage and frequency of bacillary "feedings" were less. Besides the haematogenous pulmonary foci, extension of the parenchymal process was hastened by the rupture of a caseous bronchopulmonary node, with massive discharge of bacilli into the main bronchus. The posture of the patient probably accounted for the massive implantation of organisms into the left lung. The pericardium was involved most likely by direct extension from the caseous mediastinal lymph nodes, and which secondarily invaded the myocardium. The caseous nodule in the right auricle, which invaded the muscle layer, extended from a caseous anthracotic bronchopulmonary node.

Comment on clinical findings: The X-rays of May and July gave illuminating clues as to the sequence of pathological events. In view of the findings in case 1 and the presence of pericarditis with extrasystoles in this case, a presumptive diagnosis of tuberculosis of the myocardium was made. We were surprised to note, however, the absence of the gross signs of congestive failure. The harsh rasping cough was probably indicative of extrinsic pressure by lymph nodes on the trachea and bronchi. There were no symptoms or signs to suggest tuberculosis of the spine, yet at autopsy a paravertebral abscess with invasion of two vertebral bodies was found. The discrepancy between clinical and pathological findings in this regard is not uncommon.

SUMMARY

1. The salient features of tuberculosis of the pericardium, myocardium and endocardium are briefly reviewed. The lesions in the heart are presented as part of the general picture of systemic tuberculosis.

2. The pertinent clinical and pathological aspects of two cases of protracted haematogenous tuberculosis with unusual involvement of the heart are presented.

3. Case 1 showed unusual caseous involvement of all the chambers except the left auricle. The pericardium was primarily involved with secondary invasion of the myocardium. The great vessels of the heart were also affected. The endocardium of the right auricle was invaded.

4. Case 2 revealed the pericardium to be the site of fibrocaseous tuberculosis with myocardial involvement. The right auricle presented a caseous nodule imbedded in the muscle layer.

In both instances, we believe that the cardiac lesions resulted by direct extension from caseous mediastinal lymph nodes.

I wish to express my indebtedness for valuable suggestions offered by Dr. Wolfgang Grethmann, Pathologist to Tuberculosis Service, Bellevue Hospital, and by Dr. A. G. Gnassi of the Pathological Department of the Jersey City Medical Center.

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THE INCIDENCE OF TUBERCULOSIS IN SILICOTICS[1]

ALTON S. POPE

In support of their thesis that the incidence of tuberculosis among workers exposed to silica dust is only slightly increased and tuberculosis is not in fact the cause of death in any large proportion of silicotics, Ornstein and Ulmar (1) have quoted data from a study on epidemiological aspects of silicosis and tuberculosis in Massachusetts (2). In table II of their paper they have applied a tentative ratio of three cases of active tuberculosis per annual death to obtain a morbidity rate, which they state is not significantly higher than the incidence found in a certain survey of food-handlers. As the death-rate from tuberculosis is admittedly the best figure obtainable for measuring the force of tuberculosis in a population, it is not apparent why this should be made less accurate by the application of a hypothetical ratio.

In reference to the statement that a mortality of 1,152 per 100,000 among stonecutters is a low death-rate from tuberculosis, a glance at the table quoted, table I, indicates that it is slightly over ten times the mortality rate from tuberculosis in the corresponding age and sex group in the same communities for that period. Nor is this the complete measure of the toll of tuberculosis in silicotics. Examination of 961 quarrymen in the same towns in Massachusetts showed that 219, or 22.8 per cent, showed roentgenological signs of silicosis. Making the reasonable assumption that the tuberculosis mortality, unconnected with silicosis, among the above union stonecutters is essentially the same as that for males of corresponding age in the community, we still have an excess of 8 tuberculosis deaths per year in that group, which may fairly be charged to less than a quarter of the 793 cutters, or roughly to 180 individuals, equivalent to a mortality rate of 4,400 per 100,000 per year, approximately 40 times the expected tuberculosis mortality.

In reference to the further statement that the incidence of tuberculosis found in stonecutters cannot be correlated with the statement that 75 per cent of silicotics die of tuberculosis, the authors seem to have lost sight of the difference in the incidence of tuberculosis in all persons exposed to silica dust and in those who actually have silicosis. On the basis of the above rates, it would take approximately seventeen years for 75 per cent of the 180 individuals with silicosis to die of tuberculosis,—

[1]From the Massachusetts Department of Public Health, Boston, Massachusetts.

not an unreasonable period, even if the average individual is over forty when he develops silicosis.

In reply to the statement that the death-rate from tuberculosis in a group of stonecutters shows no evidence of increase over a period of twelve years, it should be said that the composition of this group was subject to considerable change during the period in question by deaths and removals to other communities and by the addition of new members. In figure 3, *Epidemiological Aspects of Silicosis, etc.* (2), it is seen that the incidence of tuberculosis among granite workers rises steadily after the first ten years of exposure to silica dust. This is consistent with the finding that the peak of tuberculosis mortality in granite workers comes twenty years later than among all males in Massachusetts.

The question still remains whether the differential diagnosis between tuberculosis and silicosis can be accurately established by roentgenological examination. Anyone with clinical experience with silicosis and tuberculosis will agree with Ornstein and Ulmar as to the dependence which can be placed upon X-ray diagnosis of these conditions by the average inexperienced physician. Wide experience in this special field and a good quality of X-ray films are essential for reasonable accuracy in the diagnosis and differentiation of these two diseases, and in any large series of examinations there will be a certain number of cases in which a positive distinction between silicosis and silicosis with tuberculosis cannot be made on a single film. In the Massachusetts study referred to, the films were carefully checked by Sampson and Gardner of Saranac Lake and by Pancoast of Philadelphia. Unsatisfactory films were rejected and cases with a questionable diagnosis placed in a separate classification.

Since the original examination during the summer of 1933 it has been possible to check the roentgenological diagnosis of silicosis and tuberculosis in a certain number of these quarrymen in one city. Five with that classification have developed positive sputum, and three others who have come to autopsy all showed definite macroscopic and microscopic evidence of coexisting silicosis and tuberculosis. The fact that the diagnosis of silicosis or of silicosis with tuberculosis is often made upon insufficient evidence or by inexperienced physicians in no way detracts from the importance of silicosis as an industrial disease nor from the demonstrated frequency or seriousness of tuberculosis as a complication of silicosis.

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THE EFFECTS OF VITAMIN-D DEFICIENCY ON EXPERIMENTAL TUBERCULOSIS IN THE RABBIT[1]

MORRIS STEINER, MERIDIAN R. GREENE AND BENJAMIN KRAMER

The influence of vitamins on the pathogenesis of tuberculosis has been the subject of considerable investigation within the past few years. In a previous investigation[2] we have been able to demonstrate that a deficiency of vitamin C in the diet appears to hasten the development of tuberculosis in the guinea pig. In the present investigation we attempted to show the effect of vitamin-D deficiency on the development of tuberculosis in rabbits. Clausen (1) (1934), in an extensive review of the influence of nutrition upon resistance to infection, concludes that there is no striking experimental evidence, so far, that lack of vitamin D predisposes to infection. Much of the work on the effect of vitamin D on the pathogenesis of tuberculosis has been done on rats. (Grant *et al.* (2)). Whereas rickets can be produced with regularity in this animal, it is doubtful whether it can be infected with tubercle bacilli. The rabbit, however, represents a suitable animal for the production of both conditions, since rickets can be produced with ease and regularity in the rabbit and it can be infected with tubercle bacilli. We are not aware that experimental tuberculosis in rachitic rabbits has been studied, and such an investigation seemed warranted, as the rôle of vitamin D in this type of infection is still not definitely settled. Guinea pigs were not used in this study, as we were unable to demonstrate any evidence of rickets, after having fed the animals on rickets-producing diets for several months.

PROCEDURE

Animals: Rabbits obtained from the same farm were used; these were made up of various breeds, and included the Dutch, grays, silver martins and Himalayans. Litter mates were divided between rachitic and nonrachitic groups and the number of each sex was about equal in each group.

[1] From the Pediatric Research Laboratory of the Jewish Hospital of Brooklyn, Brooklyn, New York. Aided by a grant from Mead Johnson & Co.

[2] *American Review of Tuberculosis*, 1936, *33*, 585.

Care of the animals: The cages were of metal with the ends and top of heavy wire mesh. The floor was a removable wire screen over a removable tray. Two rabbits of the same sex were kept in a cage. All cages were soaked in 5 per cent cresol solution and scrubbed once each week. The food cups were washed in cresol solution and rinsed in water before each feeding. The animal room was large. Air was admitted through shutters and the window panes were covered with black paper. No direct sun and very little natural light had access to the room. The electric light was usually on during the day as a matter of convenience.

Vitamin-D deficient and control diets: A modification of McCollum's 4338 rachitic diet was used. The formula is the following:[3]

	per cent
Wheat (soft)	18.50
Maize	46.00
Wheat gluten	13.00
Gelatin	5.00
Rolled oats	10.00
Calcium carbonate	3.00
Rice cellulose	2.00
Alfalfa hay	1.50
Sodium chloride	1.00

The control diet was the same as that above with the addition of 15 drops of viosterol per kilo of food mixture. The wheat and yellow corn were coarsely ground and mixed with the other ingredients. This was fed *ad lib.* Each animal was also given 30–50 gm. of cabbage to stimulate its appetite. The rice cellulose and hay were added to supply needed roughage to the ration. This purchased hay had been dried indoors by an artificial process. Untreated hay has a lower vitamin-D content than treated hay (Russell, 1929 (3), Smith and Briggs, 1933 (4)). However, when a greater amount than 1.5 per cent was used the development of rickets was uncertain. Iodine in water was given once a week and fresh distilled water daily. They were fed daily except Sunday, receiving extra rations on Saturday.

Rickets: Symptoms of this deficiency developed in from four to eight weeks after rabbits weighing from 400–1300 gm. were placed on the rickets-producing diet. It should be mentioned that weight variation within a group was slight. Enlargement of the epiphyses at the wrists and ankles was apparent to the touch. The condition was verified by

[3] Groups 1A, 2 and 3 had no rice cellulose or hay in their diet. Wheat made up 20 per cent and gluten 7 per cent of the ration.

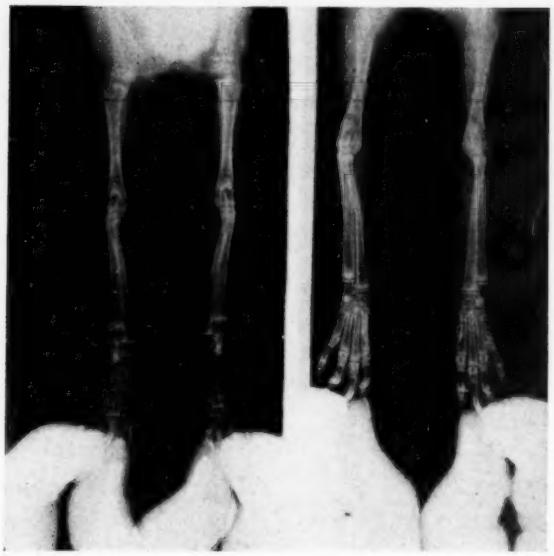

Fig. 1A Fig. 1B

Fig. 1A. Showing long bones of rachitic rabbit on vitamin-D-deficient diet
Fig. 1B. Normal bones of control rabbit on basal diet plus viosterol

Fig. 2. Beading of ribs in rabbit on vitamin-D-deficient diet

roentgenograms taken at various intervals during the experiment. Also, chemical studies of the blood showed the Ca × P product to be 30 or below. The more rapidly an animal grew, the earlier rickets made its appearance. Spontaneous healing sometimes occurred, but most animals had rickets through the first one hundred days of the experiment and many for a longer period. One rabbit had a Ca × P product of 28 at 178 days, two days before death. At autopsy, beading and fractures of the ribs and lack of calcification at the epiphysis of the tibia and fibula were noted. (Figures 1 & 2.)

TUBERCULOSIS

The inoculum: Animals were inoculated with tubercle bacilli when the rachitic condition had developed in those on the incomplete ration. Several strains of the organism were used. The human strain, H37, which produced extensive disease in guinea pigs but not in rabbits, was obtained from the Trudeau Research Laboratory. The bovine strain, B1, came from the Rockefeller Institute and strain C3 from the laboratory of the New York City Department of Health. The latter produced a rapidly fatal disease when a small dose was inoculated intravenously. Various doses were given, and the route was subcutaneous or intravenous. The organisms had been grown on the glycerine-egg medium of Petroff for three weeks when inoculated.

At autopsy, the lungs, liver, spleen, kidneys and long bones were examined grossly and microscopically, and the amount and type of tuberculosis noted. Each organ was scored according to the amount of tuberculosis present as 1+, 2+, 3+ and 4+, after the method of Petroff and Steenken (5).

Histological studies were done after staining sections by the haemotoxylin-eosin method. Tissues were also stained by Ziehl's carbolfuchsin, destained and counterstained by Gabbett's solution, and then examined for the presence of tubercle bacilli.

Complement-fixation tests: An attempt was made to determine the presence or absence of a complement-fixing antibody for the tubercle bacillus. It was hoped that a difference in the production of the antibody might occur in rachitic and nonrachitic animals. The Loomis-Kolmer modification (Willis, 1928 (6)) of the Wassermann technique was used, but results were not consistent. Perhaps with the development of a more satisfactory antigen (Rice, Orr and Reed, 1933 (7)) consistent results in the complement-fixation test for tuberculosis will be obtained.

CONCURRENT INFECTIONS

Many animals died in both rachitic and nonrachitic groups from diarrhoea; usually this was due to coccidiosis. The highest mortality occurred during the first weeks. Our experimental data includes only those animals surviving after nine weeks on the diets. The animals included in our data were not moribund. The diarrhoea was sudden in onset, and animals in good physical condition would die within one day. If any lack of resistance to tuberculosis in the rachitic group did develop it could not be attributed to a general weakness in these animals alone. The diarrhoea was common to both rachitic and nonrachitic rabbits.

Sore feet developed among some of the animals in two of our groups (2 and 3). The rabbits in these series were somewhat smaller and frequently sat in their food dishes. The diet stuck to their feet and, in trying to clean them, the animals pulled out some of the fur, thus leaving parts of the feet unprotected. Staphylococcus abscesses often resulted in these cases and the animals were quite miserable. In a few instances cold abscesses were found in the lungs.

An occasional case of nontuberculous pneumonia occurred but the incidence was no greater in the rachitic rabbits.

STATISTICAL ANALYSIS OF DATA

The mean survival periods and weights of each series of animals were calculated. It was then determined whether or not the difference between the means of the two groups being compared was statistically significant. It is sufficient to state that a statistical P is derived and the convention is to consider the difference between means significant when P is equal to 0.05 or less (8).

PROTOCOLS

Group 1: Diet controls, uninfected with tuberculosis: Two series were run at different times. Series A consisted of four rachitic animals and four rabbits receiving vitamin D in the form of viosterol. This series was concurrent with groups 2 and 3 that follow. The mean survival period of the depleted group was 135 days and that of the animals receiving a similar diet plus viosterol was 146 days. One depleted and two control animals were living when the experiment was terminated at 162 days. There was no significant statistical difference in the survival period in the rachitic and nonrachitic animal. Series B was

the control group for the remaining experiments. It included 11 animals, five of which were on the diet-producing rickets. The survival period of the latter was 125 days and that of the controls 142 days. Again there was no significant difference in survival period between these animals. The experimental period was terminated between 195 and 202 days.

Practically all animals on the ration deficient in vitamin D developed rickets in from 4 to 8 weeks. The few that did not show the condition were excluded. Around the period of 100 days, however, the rachitic lesions frequently healed. One animal in series A was still rachitic at 120 days. There was no significant difference in the mean weights of rachitic and nonrachitic animals from the onset of the experiment to death.

Rickets, produced in 4 to 8 weeks, had a tendency to heal at about 100 days. These animals did not differ significantly in their weights from nonrachitic rabbits.

Group 2: Inoculated intravenously with 0.001 mgm. strain B1: Twelve rabbits were placed on the ration deficient in vitamin D and 11 animals were given viosterol in addition to the same basal diet. X-rays at five weeks showed rickets to have developed in those animals not receiving the vitamin. At $5\frac{1}{2}$ weeks all animals were inoculated intravenously with 1 cc. of a saline suspension containing 0.001 mgm. of strain B1 tubercle bacilli.

The animals on the ration plus viosterol lived significantly longer (143 days) than did the rachitic rabbits (107 days). P was equal to 0.026. When each series was compared to its uninoculated control, the survival period was not significantly different. Nor were weight differences between rachitic and nonrachitic animals significant.

At autopsy a few animals in each series showed an occasional minimal lesion of tuberculosis in the lung. Even though progressive tuberculosis did not develop, it would appear that the inoculation had shortened the survival period of the rachitic animals.

Group 3: Inoculated intravenously with 0.1 mgm. strain H37: After 5 weeks on their respective rations, 6 rachitic and 6 nonrachitic rabbits were inoculated as designated. No difference between the mean survival period or weights of the two groups occurred. However, the survival period of uninoculated control and rachitic rabbits, when compared to the survival period of inoculated animals on similar rations,

was significantly longer (P = 0.052 and 0.025 respectively). It would seem that the inoculation shortened the length of life irrespective of the diet.

The tuberculous lesions found were for the most part occasional, small subpleural tubercles in the lung. The effect of the lesions was the same in both groups. Two animals receiving no viosterol had slightly more extensive involvement of the lung. There were no lesions in the spleen or bone-marrow, and only rarely did they occur in the kidney or liver. The 6 animals on the diet deficient in vitamin D had active rickets at death.

Lack of vitamin D did not increase susceptibility to tuberculosis after an intravenous inoculation with strain H37. Lesions for the most part were early subpleural tubercles in the lung. No advanced tuberculosis was present in either group.

Group 4: Subcutaneous inoculation with strain H37: Five rachitic animals and 6 showing no rickets after 4½ weeks on their respective rations were inoculated subcutaneously with 1 cc. of a saline suspension containing 3 mgm. of tubercle bacilli. The mean survival period of the animals receiving no vitamin D was 125 days and that of control rabbits was 142 days. The value of P was 0.56, showing no difference in survival period of significance. The weights at onset, 4½ and 7½ weeks, were likewise not significantly different as well as the maximum weights of each group and those at death. When these animals were compared to uninoculated rabbits on similar rations it was seen that the subcutaneous inoculation with H37 produced no difference in survival period or weights. Four of the 5 rachitic rabbits on the basal ration had active rickets at the time of autopsy; the fifth showed a healed condition.

No animal developed generalized tuberculosis. Five of 6 rabbits receiving viosterol had caseous masses at the site of inoculation, but no lesions of the lung, liver, spleen or bone-marrow. The 5 rachitic animals showed similar involvement. No visceral lesions were present in either group.

Subcutaneous inoculation of 3 mgm. of strain H37 resulted in only localized caseous lesions at the site of inoculation. The infection caused no significant weight loss or decrease in survival period. The condition of rickets did not shorten the survival period, lessen the weights nor cause a more severe or extensive tuberculosis.

Group 5: Intravenous inoculation with 0.1 mgm. of strain C3: Seven rabbits were placed on a diet lacking vitamin D, and five were given the same ration to which viosterol was added. Seven and a half weeks later these animals were inoculated. The mean survival period of the rachitic animals was 77 days, and differed only one day from that of control rabbits. P had a value of 0.68.

TABLE 1

Statistical analysis of rabbits inoculated with 0.1 mgm. of strain C3. Comparison with other groups

GROUP	SURVIVAL MEAN IN DAYS	WEIGHT MEAN IN GRAMS AT				
		Onset	4½ weeks	7½ weeks	Maximum	Death
−D+C3	77	710	988	1059	1226	1061
+D+C3	76	667	925	1064	1187	1068
P	0.68	0.58	0.022	>0.9	0.81	>0.9
−D	125	669	882	986	1448	1370
−D+C3	77	710	988	1059	1226	1061
P	0.017	0.45	0.014	0.48	0.24	0.13
−D+H37	123	607	821	935	1152	1065
−D+C3	77	710	988	1059	1226	1061
P	<0.01	0.21	0.11	0.19	0.16	>0.9
−D	142	782	925	982	1410	1248
+D+C3	76	667	925	1064	1187	1069
P	0.013	0.36	>0.9	0.51	0.34	0.33
+D+H37	114	672	896	985	1189	1059
+D+C3	76	667	925	1064	1187	1069
P	0.056	>0.9	0.87	0.67	>0.9	>0.9

−D = rachitic animals.
+D = control animals.
P = statistic, significant when less than 0.05.

However, both the rachitic and control animals inoculated with strain C3 had significantly shorter survival periods than uninoculated control animals or animals inoculated with strain H37. There was no significant difference in the weights at the termination of the experiment between the various groups. (Table 1.)

The 7 animals on the ration producing rickets had definite lesions of the deficiency, as was shown on roentgenograms taken two weeks or less before death.

At autopsy, all 5 control animals developed advanced tuberculosis. (Table 2.) The predominant lesions were in the lungs, which showed extensive caseous pneumonia. Advanced lesions were present in the spleen and kidneys and to a lesser extent in the liver. Lesions were found in the bone-marrow of one animal.

The 7 rachitic rabbits also developed advanced tuberculosis. The lesions were similar in severity, incidence and distribution to those found

TABLE 2

Autopsy findings in rabbits inoculated with strain C3, dose 0.1 mgm. (group 5)

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	KIDNEYS	RICKETS	SURVIVAL IN DAYS
Rachitic						
025	4+	0	2+	3+	R	77
026	4+	2+	4+	2+	R	83
027	3+	0−	2+	2+	R	69
029	4+	2+	3+	2+	R	78
030	4+	2+	3+	2+	R	80
034	4+	+	4+	3+	R	82
035	4+	+	4+	2+	R	73
Controls						
073	4+	0	4+	1+	NR	79
077	4+	3+	4+	3+	NR	81
080	3+	0	1+	2+	NR	69
081	3+	0	2+	2+	NR	74
084	4+	2+	3+	2+	NR	78

R = rachitic changes.
+ = amount of tuberculosis found.
0 = no tuberculosis found.
NR = no rachitic changes.

in the nonrachitic group. In both groups, death after the infection occurred within a month. It was as early as 15 days and the average survival after the inoculation was 23 days.

Group 6: Intravenous inoculation with 0.0027 mgm. of strain C3: The animals in this group had an initial weight averaging 200 gm. greater than in group 5, and rickets developed more slowly. Eight animals showed lesions of the nutritional deficiency after 6 weeks on the ration. They and 5 control animals were inoculated 3 weeks later with this smaller amount of strain C3. Lack of vitamin D caused no significant loss of weight or shortening of survival. As in group 5, a progressive

fatal infection with tuberculosis developed in rachitic and nonrachitic rabbits. After this dose of inoculum, death occurred as early as 20 and as late as 60 days, the mean average survival period being 34 days after infection.

At autopsy, 6 of 8 animals on the basal ration showed active rickets, one had healed lesions and the eighth animal showed no roentgenographic changes indicative of the deficiency.

All animals had developed extensive and severe tuberculosis. The lungs were riddled with caseous lesions. (Table 3.) Advanced tuber-

TABLE 3

Autopsy findings in rabbits inoculated with strain C3, dose 0.0027 mgm. (group 6)

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	KIDNEYS	RICKETS	SURVIVAL IN DAYS
Rachitic						
0104	4+	2+	4+	2+	R	83
0110	4+	4+	4+	3+	R	83
0121	4+	2+	4+	2+	R	75
0122	3+	3+	3+	1+	HR	61
0124	4+	4+	4+	3+	R	73
0126	4+	4+	1+	3+	?	75
0135	4+	0	4+	2+	R	75
0140	4+	3+	4+	2+	R	77
Controls						
0151	4+	0	0	3+	NR	62
0152	4+	2+	3+	2+	NR	65
1073	4+	3+	2+	1+	NR	72
0179	4+	4+	4+	1+	NR	81
0191	4+	3+	4+	3+	NR	102

R = rachitis.
HR = healed lesion.
\+ = amount of tuberculosis found.
0 = no tuberculosis found.
NR = no rachitic changes.

culosis was present in the spleen and liver, and to a lesser extent in the kidneys and bone-marrow. Two animals receiving vitamin D showed lesions in the intestine.

Intravenous inoculation with tubercle bacilli, C3, in dosages of 0.1 mgm. or 0.0027 mgm., produced a rapidly fatal tuberculosis in rachitic and nonrachitic animals. The life-span was significantly shorter than that of uninoculated rabbits or those inoculated with strain H37 on similar diets.

Group 7: Immunization with H37 followed by intravenous inoculation with C3: A: Dosage of 0.1 mgm. of C3: Nine rabbits were placed on a diet producing rickets, and eight were fed a similar basal ration to which vitamin D was added. After 4½ weeks roentgenograms showed rachitic changes in the long bones of the animals on the basal diet. All animals were inoculated subcutaneously with 3 mgm. of strain H37. This was followed 3 weeks later by an intravenous inoculation of 0.1 mgm. of strain C3.

TABLE 4

Statistical analysis of rabbits inoculated with H37 subcutaneously and 0.1 mgm. strain C3 intravenously. Comparison with unimmunized groups

GROUP	SURVIVAL MEAN IN DAYS	WEIGHT MEAN IN GRAMS AT				
		Onset	4½ weeks	7½ weeks	Maximum	Death
−D+H37+C3	97	735	1009	1049	1273	1104
+D+H37+C3	101	608	783	903	1103	941
P	0.72	0.027	0.019	0.1	0.016	0.15
−D+H37+C3	97	735	1009	1049	1273	1104
−D+H37	123	607	821	935	1152	1065
P	<0.01	0.052	0.058	0.26	0.23	0.83
−D+H37+C3	97	735	1009	1049	1273	1104
−D+C3	77	710	988	1059	1226	1061
P	0.051	0.68	0.57	>0.9	0.55	0.72
+D+H37+C3	101	608	783	903	1103	941
+D+C3	76	667	925	1064	1187	1069
P	0.018	0.40	0.17	0.17	0.55	0.29

P = statistic, significant when less than 0.05.
−D = rachitic animals.
+D = control animals.

There was no significant difference in survival period and weights between the rachitic and control animals in this group. However, these animals lived twice as long after infection as the unimmunized animals that were inoculated with strain C3 alone. The mean average survival period of the immunized group was 46 days and of the nonimmunized group, 23 days. The immunized reinfected animals in both rachitic and control groups lived a shorter time than the animals inoculated with strain H37 alone. (Table 4.)

In the immunized group on the diet deficient in vitamin D all animals

had had active rickets, but the condition was healed at the death of two of the 9 rabbits.

In five of 8 control animals, caseous nodules were present at the site of subcutaneous inoculation. All eight developed advanced tuberculosis in the lungs similar in extent and character to that in nonimmunized animals infected with the same strain, C3. (Table 5.) As already

TABLE 5

Autopsy findings in rabbits inoculated subcutaneously with H37 and intravenously with C3, dose 0.1 mgm.

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	KIDNEYS	RICKETS	SURVIVAL
Rachitic						
013	3+	0	2+	2+	R	69
014	3+	0	0	0	R	90
016	3+	0	1+	0	R	68
017	3+	1+	2+	1+	R	82K
018	2+	0	1+	1+	R	102
019	3+	0	0	3+	R	85
020	4+	0	0	2+	R	123
022	4+	0	1+	3+	HR	109
024	3+	0	0	1+	HR	138K
Controls						
051	4+	0	0	1+	NR	122
052	4+	0	1+	2+	NR	131
053	3+	0	1+	3+	NR	82K
054	4+	0	1+	2+	NR	87
055	4+	0	1+	2+	NR	115
056	3+	0	0	4+	NR	101
058	4+	0	1+	4+	NR	92
059	4+	1+	4+	1+	NR	78

R = rachitis.
HR = healed rickets.
K = killed.
+ = amount of tuberculosis found.
0 = no tuberculosis found.
NR = no rachitic changes.

mentioned, the disease progressed less rapidly in the immunized rabbits. There were extensive lesions present in the kidneys. However, the incidence of liver involvement was considerably less; only one of 8 animals had a one-plus lesion. The spleens of these immunized rabbits were only slightly involved and only one animal had a tuberculous lesion in the bone-marrow.

In the rachitic group, eight of the animals had very many caseous tubercles in the lung and one had a two-plus lesion. The kidney lesions were slightly less extensive and severe than those of nonrachitic animals. Eight animals had no liver involvement, while four of nine had no lesions in the spleen. Bone-marrow lesions were seen in one rabbit. Six had caseous masses at the site of subcutaneous inoculation.

Inoculation of rabbits subcutaneously with strain H37 appeared to confer some protection on animals in both rachitic and nonrachitic groups to subsequent intravenous inoculation with 0.1 mgm. of strain C3. In addition to a longer survival period, the protection was also reflected in less tuberculous involvement of the liver and spleen. However, the absence of vitamin D caused no significant difference in the response to immunization as judged by survival time and tuberculous pathology.

B: Dosage of 0.0027 mgm. of C3: Eight animals were placed on a ration producing rickets and five on that containing the antirachitic vitamin. Six weeks later these rabbits were inoculated with 3 mgm. of strain H37 subcutaneously, and after three weeks all were given intravenously 0.0027 mgm. of tubercle bacilli, C3. The difference in the mean survival period of rachitic and nonrachitic tuberculous animals was not significant (P was equal to 0.25), nor was the weight difference significant. If one considered the span of life from the time of the intravenous inoculation of the infecting dose, animals in both groups lived on an average of 69 days as compared to an average of 34 days in the unimmunized rabbits infected with C3 (group 6). The survival period following inoculation with 0.0027 mgm. of C3 was from 10 to 20 days longer than that after an infecting dose of 0.1 mgm. of the same strain.

At autopsy, the rachitic condition was healed in two of the 8 animals on the basal diet.

Two of the 5 nonrachitic animals had nodes at the site of primary inoculation. (Table 6.) All had extensive caseous lesions in the lungs. There was only a minimal involvement of the liver and spleen; only one animal had a two-plus lesion in the liver. Two had two-plus involvement of the spleen. All five had some kidney lesions, but not of the same extent and severity as those occurring in the group inoculated with C3 only. Two rabbits had bone-marrow lesions.

In the rachitic group, one had a nodule at the site of subcutaneous inoculation. All eight had advanced tuberculosis. Caseous pneumonia was present in the lungs. Half of the animals had minimal lesions in the spleen while none showed involvement of the liver. Five of eight

had tubercles in the bone-marrow, the intestines, or both. The kidneys were involved in each animal, but only one had advanced tuberculosis of this organ.

The absence of vitamin D from the diet caused no significant difference in the amount of tuberculosis which developed in the rachitic animals as compared to their controls. Protection conferred by the initial injection of strain H37 was equal in both groups. There was a difference in the

TABLE 6

Autopsy findings in rabbits inoculated subcutaneously with strain H37 and intravenously with C3, dose 0.0027 mgm. (group 7B)

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	KIDNEYS	RACHITIS	SURVIVAL
Rachitic						
0108	4+	0	0	2+	R	148K
0113	3+	0	0	1+	HR	148K
0114	4+	0	0	2+	R	110
0132	4+	0	1+	2+	HR	148
0133	4+	0	1+	2+	R	130
0138	4+	0	0	1+	R	103
0184	4+	0	0	1+	R	93
0185	4+	0	1+	4+	R	134
Controls						
0157	4+	0	2+	1+	NR	148K
0160	4+	0	0	2+	NR	106
0161	3+	2+	2+	1+	NR	148K
0187	4+	0	0	2+	NR	113
0189	4+	0	0	1+	NR	106

R = rachitic changes.
HR = healed rickets.
K = killed.
+ = amount of tuberculosis found.
0 = no tuberculosis found.
NR = no rachitic changes.

amount of tuberculosis that developed between the immunized and non-immunized animals. The immunized animals had a significantly longer survival period in both the rachitic and control groups and developed considerably less tuberculosis of the liver, spleen and bone-marrow than the nonimmunized rachitic and control animals.

DISCUSSION

On our ration, clinical rickets developed and the condition was verified by roentgenograms and blood chemistry, and, at autopsy, by bone-sections. The Ca x P product of the blood was 30 or less. When the

condition spontaneously healed, this ratio immediately jumped to a higher figure, even though the diet had not been changed, and the variations of this higher ratio were similar to those found in animals on the diet supplemented with viosterol. It seems to be difficult to maintain a persistent state of rickets over a long period of time, for the disease tends toward spontaneous healing, as indicated by blood chemistry and roentgenographic examinations.

The rachitic condition apparently did not cause a decrease in weight. In fact, the development of this disease is only apparent in growing animals. The faster the rabbit on the diet deficient in vitamin D grew the sooner the lesions appeared. Animals receiving either this ration or one similar but supplemented with viosterol did not grow quite as well as did rabbits fed on the normal diet for this species.

As will be seen in the reviews of Clausen (1934 (1)) and Robertson (1934 (9)), considerable work has been done to determine whether or not a deficiency of vitamin D causes a decrease in resistance to infection. One of us (Greene, 1933 (10)) found rachitic rabbits to be less resistant than controls to inoculation with *B. lepisepticum* and to the pneumococcus, as judged by the incidence of infection and the rate of mortality. In our present study we were dealing with a more chronic type of infection, the experimental period being considerably longer. In only one group (2) did the rickets appear to have shortened the survival period of animals inoculated with tubercle bacilli, and in this group death was not due to tuberculosis, as only minimal lesions were observed at autopsy. Therefore, with one exception, rachitic animals inoculated with tubercle bacilli did not have a shorter span of life than did inoculated rabbits receiving vitamin D.

Strain B1, a bovine strain of tubercle bacillus, proved to be relatively avirulent in our experiments. Generalized tuberculosis did not develop in either the rachitic or control animals after intravenous inoculation of this organism. In using strain H37 we hoped to produce a more chronic disease that would resemble the type found in man. Only small localized lesions developed at the site of inoculation. The absence of vitamin D from the diet did not cause a more widespread disease in the rachitic animals.

Strain C3, inoculated intravenously in large and small doses, produced extensive widespread disease in both rachitic and control animals. Here again the absence of vitamin D in the experimental group appeared to have no effect upon the severity of the process found at autopsy.

In group 7 we attempted to test the effect of vitamin-D deficiency on the immunity which developed subsequent to the subcutaneous inoculation of strain H37. Large and small doses of the virulent bovine strain C3 were used as the reinfecting agent. In neither case were we able to demonstrate any difference in the protection afforded by the primary inoculation of strain H37 in the rachitic and control animals in this group. However, when these animals were compared with the non-immunized rabbits, both rachitic and control, the life-span in the immunized group was doubled and the incidence and severity of tuberculosis in the liver, spleen and bone-marrow was decidedly less. A partial immunity to reinfection was thus afforded, which, however, was just as great in the rachitic as in the nonrachitic group.

CONCLUSIONS

1. Rickets caused no significant decrease in the weight or in the survival period of tuberculous rabbits.

2. Rachitic animals, infected with the less virulent B1 and H37 strains of tubercle bacilli or with a virulent strain, C3, showed no greater incidence of infection or any more extensive or severe tuberculosis than did control rabbits.

3. The amount of protection afforded by a primary inoculation with strain H37 to reinfection with strain C3 was the same in rachitic and nonrachitic animals.

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THE EFFECT OF IRRADIATED MILK COMPARED WITH VITAMIN-D OILS ON INHALATION TUBERCULOSIS OF GUINEA PIGS[1]

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This study was a continuation of the experiments carried on at the Trudeau Research and Clinical Laboratory, under a grant from the Wisconsin Alumni Research Foundation, by Drs. D. F. Loewen and W. H. Oatway in 1934.[2] The results in the first two series of animals fed with irradiated milk of low vitamin-D content were virtually negative so far as any influence on the evolution and progress of tuberculosis was concerned.

While 50 animals were used for each group of control and treated animals in the first experiment, it was considered possible that a repetition of the experiment, using 100 animals and a higher (double) vitamin-D content of the milk would be more convincing evidence for or against any direct or indirect influence on the disease.

Furthermore, if the superiority of irradiated milk for the nutrition of tuberculous patients was to be demonstrated, it was important to compare it with oils containing the same or much higher vitamin-D potency than that used in the first series. It might thus be shown whether or not the vitamin-D in the milk was an important factor, provided the control animals were fed with like proportions of powdered skim-milk with the oil.

Hence the following plan was prepared to supplement the original experiments: Four hundred full-grown guinea pigs were segregated into 4 groups of 100, to be fed and inoculated in the same manner as in the previous experiments.

Group I: Fed with a daily ration of twice irradiated cream, 80 per cent butter fat. The maximum ration allowed for each guinea pig, weighing 500 gm., was 6 gm. of cream containing 10 Steenbock units or 33 U. S. P. of vitamin D. The quantity fed was varied proportionately each week to the average weight of the animals in each cage of five.

[1] This work was undertaken under the direction of Dr. S. A. Petroff, who was obliged to leave during its progress.

[2] *American Review of Tuberculosis*, 1936, *33*, 733.

The cream was mixed with 2.4 gm. of dry skim milk powder and 6 gm. of fresh chopped carrots per guinea pig as in the former experiment. The mixture was fed in the morning, followed in the afternoon by a liberal portion of hay and about 44 gm. of oats.

Group II: Fed as in group I, but with nonirradiated milk (cream) from the same source.

Group III: Began with codliver oil (Parke Davis & Co.) and followed by tuna liver oil (Abbott) in place of cream; maximum dosage of vitamin D the same (0.24 cc. of codliver oil or 0.018 cc. tuna oil per 500-gm. pig.)

Group IV: Same as in group III, except that the ration of oil was ten times greater, namely 2.4 cc. codliver oil or 0.18 cc. tuna liver oil per 500-gm. guinea pig (100 Steenbock vitamin-D units).

The cream was kindly furnished by the Borden Food Products Co. and was twice irradiated but without changing the taste. The vitamin-D assay was made at the University of Wisconsin, and contained in the 80 per cent cream an average of 1,500 units per quart.

The oils were also of high potency, but the tuna liver oil was substituted for codliver oil after the first month because of the apparent disinclination of the animals to ingest the latter and because of the smaller dosage required. It was kindly contributed by the Abbott Co. It was realized that the other ingredients of the diet contained both vitamin D and large amounts of A (carrots and oils). An assay sample of the hay used in feeding showed no potency of vitamin D in the amount fed. The mixtures were weighed for each cage of 5 animals according to their average weight at the beginning of the feeding.

The animals were tuberculin tested and caged equally according to sex and weight as in the first experiments. The chart indicates the weight changes: Group I weight, average 441 gm.; Group II weight, average 413 gm.; Group III weight, average 416 gm.; and Group IV weight, average 417 gm. The animals' normal diet consisted of carrots, oats and hay. The special diets were begun two weeks before infection and gradually increased from 1 to 10 units of vitamin D in groups I and III and to 100 units in group IV.

The infection was with a virulent H37 culturesuspension, containing an average of one bacillus to the oil-immersion field and sprayed into the inhaler described in the previous paper.

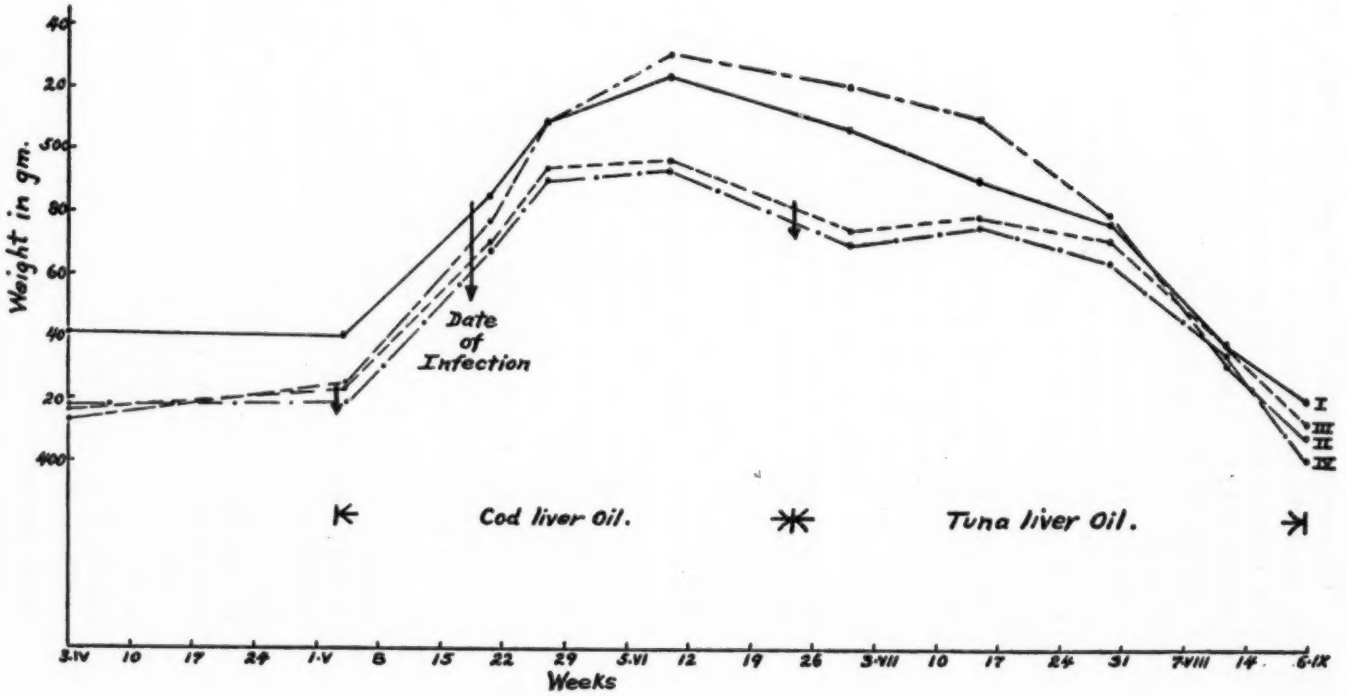
Tuberculin skin tests after 30 days showed 100 per cent infection, which was later confirmed at autopsy.

Altogether, 41 animals died of causes other than tuberculosis: 11 un-

Number of animals in each group weighed to make up averages.

	3·IV	6·V	26·V	27·V	10·VI	1·VII	15·VII	29·VII	12·VIII	6·IX
I	100	100	100	100	100	98	95	92	80	67
II	100	100	100	100	100	99	98	96	82	67
III	100	100	100	100	100	100	94	92	79	73
IV	100	100	100	100	98	97	91	80	66	56

Weight Chart



determined, 11 of gastroenteritis, and the balance of intercurrent infections, 10 being due to pneumonia chiefly of *Bacillus Friedländer* origin.

Eighty-eight animals died of tuberculosis during the first 80 days following the infection. The majority manifested early generalized disease after 10 weeks; so it was decided to terminate the experiment after 80 days. In recording the findings, a scale of one to four plus was used to indicate the extent of disease in the lungs, spleen, liver and lymph nodes. It was found that in the animals that died of tuberculosis little or no difference could be noted in the lesions. (Table 1.)

Of those killed, all but group IV seemed to have nearly uniform generalized tuberculosis. The fourth group revealed smaller areas of caseation and splenic enlargement than the others. On the other hand, the deaths from other causes and from tuberculosis as well had been three times as frequent in this group and they seemed to have poor tolerance

TABLE 1

Degree of tuberculous involvement

GROUP	LUNGS	LIVER	SPLEEN	LYMPH NODES	NUMBER OF GUINEA PIGS
Irradiated cream, I	6.3	6.5	7.3	7.3	99
Nonirradiated cream, II	6.8	8.0	8.8	7.8	98
Low-concentration oil, III	5.0	6.3	6.5	7.0	100
High-concentration oil, IV	5.3	6.0	7.3	6.4	97

Scale: one to ten plus.

for the oil diet. Ether extracts of their faeces, made several times, did not, however, show unabsorbed oil, nor were their carrot portions uneaten.

The hot weather in June, combined with the larger ration of oils, undoubtedly combined to diminish their appetite.

In all animals there was evidence of tracheobronchial and pulmonary tuberculosis with beginning spread into the liver and spleen.

Thus it cannot be said that this mass experiment produced evidence of any real restraining influence on the part of vitamin D upon primary-infection tuberculosis in adult guinea pigs.

Whether or not the oils containing higher vitamin-D concentrations had some toxic effect because of the vitamin was not ascertained. It appears unlikely, since the highest doses were well below the range of toxicity of vitamin D found by others for guinea pigs.

The evidences of calcium deposits, as seen by the naked eye, were sought for without success, but the short duration of the experiment would not be favorable for such deposits.

DISCUSSION

The nutrition of the animals was noted by weekly weighings and gains were maintained before infection and for a month following; then a fairly uniform loss of weight occurred as the disease spread.

In reviewing the experiment, it is apparent that the guinea pigs in group IV were not as resistant as the others. The inflammatory reactions were less acute, that is, swollen and caseous lesions, than those in the other groups. If it be thought that lessened inflammatory reaction is evidence of resistance in tuberculosis, then some influence other than allergy caused early fatal effects.

The question might be raised whether a rich vitamin-D milk diet might act favorably in preventing a primary infection from spreading in childhood while not effective in adults. The use of infant guinea pigs for such a test is hardly practicable, considering their extreme susceptibility to tuberculosis.

SUMMARY

A repetition of the mass-feeding experiment with irradiated cream containing double-strength vitamin D, using 100 animals, gave no evidence of any influence of vitamin D on the development and course of inhalation tuberculosis in adult guinea pigs. The lesions in the groups of guinea pigs fed on irradiated and plain cream were of the same type.

Codliver and tuna liver oil, used in the same dosage of vitamin-D units as used in the irradiated cream groups, and also in graded dosage, produced no differences in the lesions as found in the cream-fed animals. The diet was not well tolerated, however.

In tenfold doses (vitamin D) the feeding of these oils was less well borne and one-third of the animals died before ten weeks. The survivors when killed gave evidence of toxaemia, but showed smaller spleens and less caseation, but no calcification.

The effect of vitamin D *per se* is questionable in the last group.

A NOTE ON THE EFFECT OF SYNTHETIC ASCORBIC ACID (VITAMIN C) ON THE GROWTH OF THE TUBERCLE BACILLUS[1]

CHARLES H. BOISSEVAIN AND JOHN H. SPILLANE, JR.

Natural vitamin C tends to increase the ability of guinea pigs to combat tuberculosis, according to several workers. When it is withheld from the animals, the disease is said to be rapidly fatal (1). On the other hand, the administration of large quantities is reported (2) (3) (4) to prolong the life of the infected animals. The spread of the lesions, however, does not seem to be affected by giving the vitamin (5). Since synthetic ascorbic acid is commercially available, a study of its effect on the growth of tubercle bacilli was undertaken.

Synthetic ascorbic acid (*Redoxon*, Hoffman-LaRoche) was added in various concentrations to artificial media which were then inoculated with the H37 strain of tubercle bacilli. Growth occurred in the media originally containing less than 0.5 per cent ascorbic acid, at which concentration the reaction was too acid for growth (pH 4.3). It was found by the method of Bessie and King (6) that growth occurred only after the ascorbic-acid content had fallen below 0.001 per cent.

To avoid the pH change, the sodium salt of synthetic ascorbic acid was used in another series. In one group of media the vitamin content was maintained by determination of the ascorbic acid every three days and addition of the vitamin when necessary. It was found that, although the pH remained within the range compatible with growth, the tubercle bacilli did not grow in the media in which the vitamin concentration was maintained at the level of 0.001 per cent or higher.

The results seemed to warrant animal investigation. Six guinea pigs were inoculated with 0.05 mgm. H37 tubercle bacilli, and four of them received 25 mgm. synthetic ascorbic acid (as the sodium salt) subcutaneously each day for three weeks. This quantity is fifty times the antiscorbutic dose. At the end of the period all animals had tuberculous lymphadenitis, and they had all lost weight. There was no difference

[1] From the Laboratories of the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

in the percentage weight loss between the animals receiving the ascorbic acid and the controls. The animals were killed, and at autopsy all of them had tuberculous involvement of the liver and spleen.

CONCLUSIONS

1. Synthetic ascorbic acid in a concentration of 0.001 per cent inhibits the growth of human tubercle bacilli in artificial media, although the hydrogen-ion concentration of the media is suitable for such growth.

2. The daily injection of fifty times the antiscorbutic dose of synthetic ascorbic acid does not protect guinea pigs from infection with human tubercle bacilli.

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THE THERMOLABILITY OF THE TUBERCLE BACILLUS[1, 2]

H. J. CORPER AND MAURICE L. COHN

An exact knowledge regarding the reaction of the tubercle bacillus to temperatures of various grades was previously essential to the field of bacterial culture of these bacilli and to the field of preventive medicine because of the pasteurization of dairy products. Thus, much knowledge was gained, although in these fields a wide latitude of experimental possibilities existed without resorting to sharply delimiting details. However, with the advent of preventive inoculation against tuberculosis and the natural aversion to the use of viable products of possible unstable bacterial strains, the exact study of the effect of heating these bacteria and of still preserving their antigenic properties again assumed importance. Likewise, a knowledge of the exact thermal death-point takes on practical significance with the advent of reputed hyperpyrexia therapeutic results in human disease.

The tubercle bacillus ranks almost alone in certain striking characteristics in producing a disease entity of individual nature and in displaying peculiarities hardly expected from pathogenic bacteria. It possesses a high resistance to exposure to acids and alkalies (1), can remain viable over long periods of time under favorable conditions both in the animal economy and in the test-tube (2), and displays in many respects a resistance characteristic of spore-forms, although it is reputed not to produce spores. A particularly high vacuum (one billionth of an atmosphere) and drying over one of the most avid chemical water-removing substances (phosphoric anhydride) fails to ensure the loss of viability of the tubercle bacillus (3). Similarly, the continued exposure to the temperature of liquid air (about $-180°$C.) for weeks fails to ensure death of the bacilli (4).

Although there is an exhaustive literature on the thermal death-point of tubercle bacilli under various conditions, and particularly with milk and dairy products, much of these data have resulted from work per-

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] Presented at a session of the Pathological Section, 32nd annual meeting, National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

formed before the methods of preparing fine suspensions of tubercle bacilli were standardized (5) and before the significance of hydrogen-ion concentration and buffered solutions were stressed (6), while some of the tests were done on natural tuberculous materials open to the criticism of being irregular heavily infected specimens of unknown nature. Also, all the conditions of uniformity throughout the test material were not adhered to until more recently.

In a study on the biology of the tubercle bacillus, Weinzirl (7) tried to answer the question whether the so-called fatty capsule served to protect these bacilli, and, although not able to give a final answer, he found that the fat does not materially increase the resistance of the bacilli

TABLE 1

Previous attempts to determine thermal death-point of tubercle bacilli

INVESTIGATOR		TEMPERATURE	LETHAL TIME
DeMan	(1893)	55°C.	4 hours
Yersin	(1888)	60°C.	10 minutes
Bonloff	(1892)	60°C.	20 minutes
Forster	(1892)	60°C.	6 hours
DeMan	(1893)	60°C.	1 hour
Schroeder	(1894)	60°C.	15 minutes
Woodhead	(1895)	60°C.	a. 8 hours
			b. 45 minutes
Theobald Smith	(1899)	60°C.	15–20 minutes
Russell and Hastings	(1900)	60°C.	20 minutes
Hesse	(1901)	60°C.	20 minutes
Rosenau	(1907)	60°C.	20 minutes
Delepine	(1914)	64°–92°C.	over 39 minutes
Campbell Brown	(1923)	60°C.	20 minutes
		70°C.	5 minutes

to chemical and physical agents. Heat at 60°C. in a water-bath after 30 minutes killed neither fat nor lean bacilli, while, after 60 minutes, in two out of six tests, the specimens were killed (1 lean and 1 fat).

Most of the earlier work on the thermal death point of tubercle bacilli was primarily concerned with the efficiency of pasteurization of milk, and thus the lower ranges below 60°C. were not accurately studied. Many observations were also crudely performed and inadequately controlled, in many cases yielding data of limited value. Confusion and polemics were common. However, a careful survey of the data in consideration of present observations permits a tabulation of past data

so that it may be evaluated. In a carefully controlled critical investigation on the thermal death-point of the tubercle bacillus in milk in 1923, Campbell Brown (8) presented a brief tabulation of the important earlier data for temperatures at 60°C. or over, part of which is reproduced in table 1. He claimed, as a result of a personal study with 25 strains of tubercle bacilli, that the wide variation in results in the past had been due to too little care in carrying out the experiment and to the fact that the lesions caused in test animals had previously not always been given sufficient time to develop and be accurately diagnosed. He found no wide difference in the thermal death-point regardless of strain or type of bacilli, 60°C. requiring twenty minutes and 70°C. five minutes.

More recently (1925), Oerskov (9), studying tubercle bacilli at five-minute intervals for 50 minutes at 63°C., found by culture method on Petroff's medium that it took 35 to 45 minutes to obtain negative results.

In 1927, Meanwell (10) found that 62.8°C. for 30 minutes did not invariably kill tubercle bacilli in naturally infected milk, although in most cases it did. At 60°C. for 20 minutes, tubercle bacilli are in many cases destroyed, but this time and temperature leave no margin of safety.

In a more detailed investigation on milk in 1928 and 1929, Katrandjieff (11) found that normal and fat-free milk, kept at 58°C. for 30 minutes, with a pH of 6.3–6.7, was still positive for viable tubercle bacilli by animal test; while with defatted milk at 58°C. for 30 minutes and pH 6.0, and at 63°C. for 30 minutes and pH 6.0, 6.3, and 6.7, fat-free or not, the animals tested did not become infected. At 58°C. for 30 minutes and pH 6.0, 6.3, and 6.7, the presence of sugar in milk did not prevent infection of animals. At 60° to 63°C. for 30 minutes, the presence of sugar resulted in attenuated infections only. The degree of acidity pH 6.0 associated with chemical substances resulting from heating to 63° for 30 minutes in the presence of saccharose seems to play an important part in the destruction of tubercle bacilli. Even as late as 1933 (12), irregular and inconsistent results are found in the literature because uncontrolled methods and lack of a good criterion of death had been used.

Recently, with the wave of enthusiasm over the successful use of artificial hyperpyrexia in other fields of medicine, the thermal death-point of the tubercle bacillus has again assumed importance, especially as regards the possibility of killing this organism in the body by judi-

ciously applied general or local heat. In 1933, the application of hyperpyrexia to 5 cases of human tuberculosis was reported, and it was concluded that "there is some definite value in hyperpyrexia as applied to pulmonary tuberculosis." At this time there was no other proof available "save the fact of X-ray and clinical improvement (13)." Following this, a further report in 1935 (14) showed 19 human cases treated with general diathermy, with 16 showing X-ray improvement, 2 cases with no change, and 1 case aggravated. In addition, the report gives the results of subculture data on Herrold's glycerin-egg medium. Five strains of human tubercle bacilli grew luxuriantly from 96° to 100°F. inclusive; poorly from 102° to 104°F.; and not at all above this temperature. Five strains of bovine tubercle bacilli grew luxuriantly from 96° to 104°F. inclusive; poorly from 106° to 108°F.; and in only one tube out of 15 at 110°F. Two strains of avian tubercle bacilli grew luxuriantly from 96° to 108°F. and poorly at 110°F. *M. leprae* grew luxuriantly from 96° to 110°F. Two human strains, incubated for 3 weeks at 106° and 108°F., were still able to produce progressive disease in guinea pigs. These strains after three weeks' incubation at 110°F. caused no tuberculosis in 44 days in guinea pigs.

Within the past year (1935), Anderson (15) recorded observations on *Mycobacterium leprae muris*, correlating Denny's work on hyperpyrexia in leprosy. Leproma tissues of the rat were used, and it was found that temperatures in excess of 43°C. for five hours were required to kill *M. leprae muris in vitro*, rats being used as test animals to determine viability. Exposure at 50°C. for five hours seemed sufficient to attenuate this mycobacterium.

PRECAUTIONS AND DESCRIPTION OF APPARATUS

There are many obvious criticisms of both the methods and data available as to the thermal death-point of tubercle bacilli as one reviews the recorded findings in the literature. In the earlier data, the lack of large supplies of animals for detailed tests is an acknowledged handicap, but, with the perfection of adequate culture methods, this dwindles into insignificance (16). However, in most cases, reports take no cognizance of the pH factor (17), and no comparison is made between milk and isotonic buffered salt solutions. In addition, the temperature is not adequately controlled, in that it is taken for granted that the mere placing of a receptacle in an incubator or water-bath guarantees the exact temperature of the contained liquid or contents in any part of this

incubator. Commonly also, the time-factor of heating up a cold solution is entirely overlooked. The number of bacteria present was given, in most cases, absolutely no consideration. Many times, also, only one temperature was studied, giving no clue as to the lethal-curve, time and temperature relationship, which would in addition serve as a control on errors otherwise easily overlooked when only one temperature was studied. In all the reports available to us, one or more of these criticisms seemed to apply.

In our earlier work, which was primarily concerned with determining the lethal time temperatures for suspensions of tubercle bacilli to be used for immunizing purposes, we encountered errors and obstacles which had to be overcome. Among these was a change in reaction consequent to even low heating when physiologic salt solutions were used. This is well illustrated in the decided lowering of the pH from pH 7.0 of 0.9 per cent sodium-chloride solution and a consequent shortening of the lethal time due to the acidity. This led to the substitution of a buffered Tyrode's solution (which at times became alkaline on heating) and finally the use of Long's liquid medium (from which asparagin and glycerol were omitted). This medium was set at pH 7.0 and remained fairly constant throughout long periods of heating at the temperatures studied (from 40°C. to 70°C.).

A second source of possible wide variation from recorded thermometric figures was the temperature of the medium or fluid used for test. It is a well-known but not commonly recognized fact that there can exist a wide range of variation in the temperature in various parts of an air-incubator or a water-bath not equipped with adequate stirring facilities. After numerous tests, it was found that these variations were particularly striking in short-duration experiments at higher temperatures (above 45°C.) and that the only safe method for ensuring the accuracy of recorded temperatures was by using a thermometer immersed directly in the fluid containing the bacteria being studied. When immersion is not feasible, as in certain culture experiments, easily read thermometers must be placed in close proximity to the individual culture tubes.

Another source of error pointed out by Campbell Brown concerns the original heating of the suspension fluid. He suggested having the major part of the fluid slightly higher in temperature than that desired and adding the suspension of bacilli in more concentrated form in cold (room-temperature) solution, so that, at the moment of addition, the

temperature is at the exact desired point (as determined by previous control tests). This we have found a valuable suggestion for guidance, especially where the bacilli are killed within a few hours or less. In addition, it is obvious that the number of bacilli in suspension is important. For that reason we used a heavy suspension (1.0 mgm. per cc.), a medium suspension (0.001 mgm. per cc.), and a very fine suspension (0.000,001 mgm. per cc.) for all of our tests. A number of devices were tried before the simple receptacle finally used in the experiments, to be reported, was developed to determine the effect of heat upon the suspensions of tubercle bacilli in various fluids. It was concluded that the ideal apparatus should embody the following principles: (1) the temperature should be recorded directly by immersion of a thermometer in the fluid itself; (2) the volume of fluid should be small, and not excessive, to ensure uniform heating and still large enough to allow removal of specimens without decided volume change and change of temperature; (3) the experiments should be performed with the exclusion of light; (4) the thermostatic control should not vary appreciably during the course of the tests as indicated by the temperature of the fluid; (5) the entire outfit should be easily sterilized and maintained thus throughout the experiment; (6) the entire apparatus must be heat exposed (so-called submerged) to ensure equal heat treatment of all parts of the apparatus and bacillary suspensions.

The test-chamber used by us consists of a pyrex-glass flat-bottom tube, 8 cm. tall and 4 cm. in diameter (cylindrical shaped). At the top, a slight flange or rim is made, so that the vessel can be suspended in the can used for the purpose of excluding light from the bacilli. This tube is fitted with a number-8 rubber stopper with 3 holes; through the larger hole (about 2 cm.) is inserted a glass tube, flanged at the top, and into this is inserted a cork through which the sampling pipette passes into the test-fluid. The cork is tightly fitted to the pipette, being removed with the pipette at every withdrawal of a sample; through one of the two smaller holes in the rubber stopper, a long thermometer passes into the test-fluid; while through the second small hole a small glass tube plugged with cotton passes just below the rubber stopper, so as to act as an air-vent to relieve pressures. The glass test receptacle is supported by the glass rim at the top, in a tin can, without, however, touching the bottom or the walls of the can,—the can acting as an air-bath, and dark chamber. The entire apparatus is placed in an automatically regulated air-incubator, heated electrically and

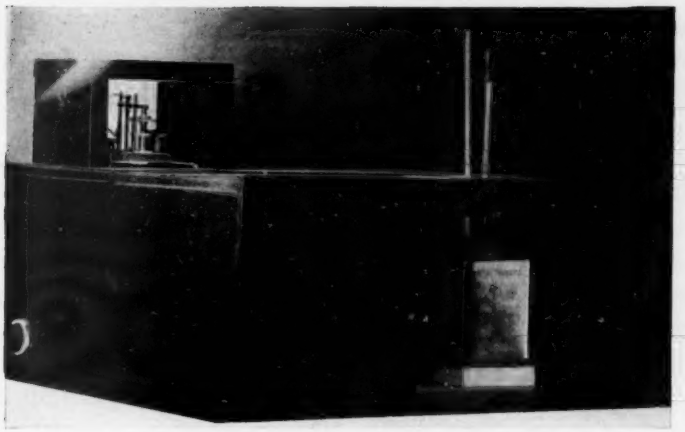


Fig. 1. Automatically regulated heat-chamber used for studying the survival of fine suspensions of tubercle bacilli at various temperatures. Through the front door in the chamber (which is closed during runs) is shown the can in which the glass reaction receptacle is suspended (the rubber-stopper type is shown here), with thermometer and sampling pipette passing through a sliding glass door in the top of the heat-chamber.

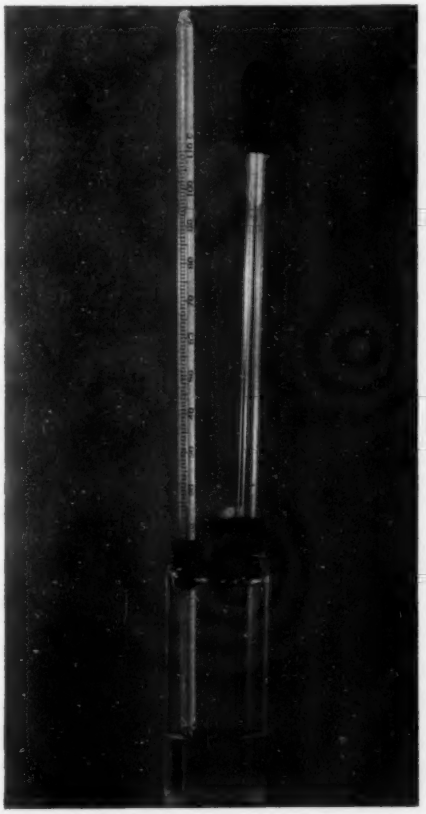


Fig. 2. The rubber-free glass reaction receptacle made of pyrex glass with two holes in the top. Through the smaller one is shown the thermometer with cork (bacterial seal). Through the larger hole is shown the sampling pipette passing through a cork (bacterial seal) with single hole plugged with cotton to act as air-vent. The cork is tightly fitted to the pipette, so that, when the pipette is removed for sampling, the cork is carried with it. This form of apparatus was finally adopted to avoid the use of rubber, and is easily sterilized.

maintained at constant temperature at the regulator and incubator thermometer, not varying more than 0.5° throughout runs extending over weeks.

The glass receptacle is sterilized by dry heat after the addition of a few drops of pure ethyl alcohol. The pipette and cork stopper are sterilized in the same way, while the rubber stopper, thermometer, and tube with cotton plug are completely submerged in a mixture of equal volumes of pure ethyl alcohol and pure acetone for two hours, after which the alcohol and acetone are evaporated off in a dry sterilizer at about 80°C. This treatment assures absolute sterility of the apparatus, if properly conducted. In order to conduct a test, about 9 cc. (or twice this amount) of the fluid (Long's solution) is placed in the glass chamber, after which the apparatus is assembled and warmed. It is then placed in the can container and is allowed to come to temperature equilibrium. When ready to add the suspension of the bacilli (which is 10 times the desired concentration), the liquid in the container is allowed to heat about 2.5°C. higher than the final desired temperature. This is done by short-circuiting the regulator for a short time and allowing the entire air-chamber to heat to the point desired. The bacillary suspension is now added in 1-cc. amounts, if 9 cc. of fluid was used (or 2 cc. if 18 cc. was used), at the same time removing the incubator short-circuit. A sample for control is taken immediately on stirring the mixture and thereafter at appropriate intervals. In our experience, this procedure results in an immediate temperature adjustment and assures the exposure of the bacilli to the desired temperatures, which are controlled by checking the thermometric readings until equilibrium is assuredly established. With this arrangement of apparatus, there is no drop in temperature of the liquid in the test-chamber. Immediately upon removal of the sample, it is planted on the culture medium which ensures complete discontinuance of heat treatment. To ensure a quick return of the pipette, the entire sample may be run into one cold culture tube and two others planted from this. In view of the likelihood of error through the use of rubber stoppers, due to development of possible volatile toxic materials over long periods of heating, our experiments were controlled by finally using rubber-free glass receptacles, but the results obtained were identical with those in which the rubber stoppers were used, indicating that either form of apparatus is suitable for such tests when properly performed.

THE EFFECT OF HEAT IN VITRO ON TUBERCLE BACILLI

The effect of heat *in vitro* on tubercle bacilli was studied in two ways and for practically two different purposes. The first was to determine the effect of various degrees and times of heat exposure on fine suspensions of human tubercle bacilli, using both avirulent and virulent strains. A great many tests were performed in an effort to perfect the technique and to obtain the final survival curves, but it will suffice here to present only the final results in a well-buffered, isotonic solution showing no appreciable changes throughout the period of experimentation and to note the tests which had to be improved upon to obtain more perfect

TABLE 2

The survival time for avirulent and virulent human tubercle bacilli in fine suspension in a modified Long's liquid medium at various temperatures

TEMPERATURE	MILLIGRAMS OF TUBERCLE BACILLI IN FINE SUSPENSION PER CUBIC CENTIMETRE	
	1.0	0.001†
42°C.—107.6°F.	Indefinitely	Indefinitely
45°C.—113°F.	8 days (to 20 days*)	2 days (to 6 days)
50°C.—122°F.	5 hours	45 minutes (to 3 hours)
53°C.—127.4°F.	1 hour	10 minutes (to 20 minutes)
55°C.—131°F.	15 minutes (to 30 minutes)	5 minutes (to 10 minutes)
60°C.—140°F.	Not at 5 minutes	Not at 5 minutes

* Since these data are an average of a number of experiments, the average survival time is presented for a number of cases. Occasionally, for unexplained reasons, a test would give a survival time extending to the second noted interval, given in parentheses, even though young actively growing cultures (about one month) were used for making the suspensions.

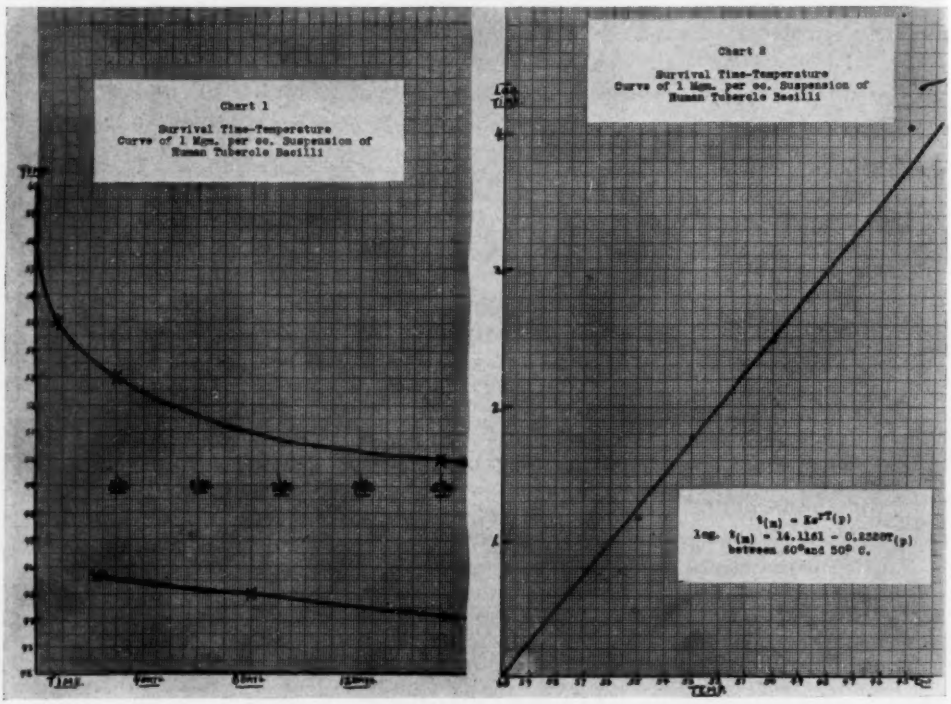
† The tests included the 0.000,001 mgm. per cc. dilution, but this is not recorded in this table, since the small number of bacilli proved more susceptible to the heat, and, especially at temperatures over 50°C., immediate contact with heat prevented positive cultures.

results. Isotonic physiological salt (sodium chloride) solution and certain so-called buffer solutions were found unsuited for these tests because the pH would change during the heating period. The use of capsules or ampules was considered undesirable, since all tests in a series should be carried through on the same suspension if possible. Extraneous influences, such as the presence of chemicals disclosing change under the influence of heat should be avoided. Finally, we chose as a satisfactory solution with no apparent disadvantages a solution (a modified Long's medium) maintaining a pH of about 7.0 (after adjustment) and composed of the following: ammonium citrate, 5 gm.; potassium

acid phosphate, 3 gm.; sodium carbonate, 3 gm.; sodium chloride, 2 gm.; magnesium sulphate, 1 gm.; ferrous ammonium citrate, 0.05 gm.; water to 1 litre.

With this isotonic buffered neutral solution, using fine suspensions of tubercle bacilli, and assuring immediate heating of the bacilli with a maintenance of an accurate temperature throughout the experimental period, the results recorded in table 2 were obtained.

It is evident from the findings recorded in table 2, that, in fine sus-



pension and in a well-buffered medium, human tubercle bacilli can survive (for months) at 42°C., and this circumstance will be elaborated upon in the growth experiments; while at 45°C. they survive for about 8 days in the 1-mgm. suspension, and 2 days in the 0.001-mgm. suspension. It appears from this that, the greater the number of bacilli present, the longer the survival period. At temperatures above 50°C., the survival is a matter of hours only. No appreciable difference was noted for avirulent or virulent strains.

If we now plot the curve of survival of the 1-mgm. suspensions, we find that there is an abrupt drop from almost immediate loss of viability at 60°C. to a survival period of 5 hours at 50°C. and a gradual loss of viability to 42°C., at which temperature death of the bacilli due to heat practically does not occur. (Chart 1.) When the logarithm of the survival time is plotted against the temperature (as in chart 2), a straight-line curve is obtained, indicating that the viability is a logarithmic function of time and temperature. Thus, between the temperature of 50° and 60°C., survival of the bacilli follow "the law of organic growth," "t" = Ke^{rT}, where "t" is the time, "T," the temperature, and K and r are constants. When the constants are determined, the equation becomes log. t = 14.1161 − 0.2328 T. This equation only holds for the temperature range a little below 50°C. After this temperature, the bacilli die very slowly, and at 42°C. may survive.

TABLE 3

The effect of incubation at 42°C. on the growth of human tubercle bacilli

TEMPERATURE*	MILLIGRAMS PER CUBIC CENTIMETRE IN FINE SUSPENSION USED FOR SEEDING CULTURE TUBES		
	1.0	0.001	0.000,001
37.5°C.— 99.5°F.	2†	3	4
42°C. —107.6°F.	2	3	4

* The temperature recorded is that obtained from a thermometer placed in close proximity to the culture tubes contained in a covered tin can.

† The numeral given indicates the number of weeks when the first appearance of growth was noted on the culture-tubes (4 tubes being used for each planting).

THE EFFECT OF HEAT ON THE GROWTH OF TUBERCLE BACILLI

The second determination of the effect of heat on tubercle bacilli was to discern its influence upon the growth of the bacilli on culture media; and, within the limits of our experimental tests, it was found that on good nutrient media, such as inspissated egg-yolk, the bacilli were able to grow at a temperature at which they could survive the effect of the heat in fine suspension in a neutral well-buffered solution, provided conditions for growth, such as isotonicity, hydrogen-ion concentration, water and air balance (18), etc., were carefully maintained at this temperature. Such an illustrative experiment is recorded briefly in table 3 for human tubercle bacilli.

The difficulties encountered in culture experiments at 42°C. concerned

primarily the prevention of drying of the nutrient medium. To learn to overcome all the difficulties, it was necessary to develop a technique peculiar to the situation, and required innumerable repeated experi-

Fig. 3. Photograph of cultures of human tubercle bacilli at 37° and 42°C. after 6 weeks, and planted on inspissated egg-yolk medium, using fine suspensions containing 1 mgm. per cc. (the two left tubes), 0.001 mgm. per cc. (two centre tubes), and 0.000,001 mgm. per cc. (two tubes at the right). Note the excellent growth in all tubes and the drying of the media at the top, with plenty of water at the bottom in the 2nd, 4th, and 6th tubes from the left, 42°C. Note also the method of maintaining water-balance in all the tubes by the use of well-paraffined cotton plugs, corks (not paraffined), and finally tin-foil capping.

ments, especially since our technique of culturing tubercle bacilli was developed for temperatures around 37°C. and lasting several months. Any attempts to maintain moisture balance from the outside resulted

only in mold difficulties. A peculiar and interesting phenomenon was noted at the higher temperatures in that frequently the top of a slant of inspissated egg-yolk medium would become completely dried out, with a satisfactory intermediate zone, and this in spite of the presence of adequate liquid in the bottom of the culture-tube (see photograph). When one explains this on the basis of physicochemical water phenomena, it is perfectly clear that such a condition can exist in the culture-tube. It is obvious from these experiments that human tubercle bacilli have a wide latitude of ability to grow on a good nutrient medium at temperatures ranging up to as high as 42°C. (107.6°F.) and this even in small plantings of 0.000,001 mgm. of fine suspension.

TABLE 4

The effect of pyrexia treatment on human tubercle bacilli in the rabbit's ear

TESTS	MGM. TUBERCLE BACILLI IN FINE SUSPENSION PER CC. USED FOR INJECTION (0.1 CC. INTRACUTANEOUS)		PYREXIA EXPOSURE
	0.01	0.000,001	
Control Susp.	3†	4	July 18—2 hours—108.9°F.
Control Ear	4	5‡	July 23—2 hours—108.9°F.
Heated Ear*	4	5‡	July 24—2 hours—108.9°F.
			July 25—2 hours—108.9°F.
			July 26—2 hours—108.9°F.
			July 27—2 hours—108.9°F.
			July 29—4 hours—108.9°F.
			July 30—4 hours—108.9°F.
			July 31—4 hours—108.9°F.
			Total 24 hours

* Radio waves, 60 metres (5,000 kilocycles), were used as a source of heat.

† The numeral indicates the number of weeks in which the first growth appeared on the culture medium (3 tubes of egg medium and 3 tubes of potato medium for each specimen).

‡ Only one culture tube of the six used was positive.

THE EFFECT OF HEAT IN VIVO ON HUMAN TUBERCLE BACILLI

Although the foregoing studies *in vitro* strongly suggested that a temperature attainable *in vivo* would have no material deleterious influence on tubercle bacilli, it seemed advisable to do some *in vivo* tests, especially since the method of determining the viability of tubercle bacilli by culture, following intracutaneous injection, had been previously worked out by us (19) and was capable of disclosing very small numbers of viable bacilli when present in the tissues. There are a great many methods for applying both general and local heat available, but, since we were studying the effect of short radio waves on tubercle bacilli

and had found certain wave-lengths to be without effect directly upon the bacilli, we used this means for inducing local temperatures at the site of inoculation of fine suspensions of graded amounts of tubercle bacilli into the ears of rabbits. The results of such an experiment are briefly recorded, with the pyrexia exposure used, in table 4.

The results recorded in table 4 are illustrative of our inability to destroy tubercle bacilli, injected intracutaneously into the ears of rabbits, by means of local pyrexia. All types and lengths of exposure were tried, even to producing severe burns without destroying the tubercle bacilli in the tissues.

SUMMARY AND CONCLUSIONS

1. An improved method of determining the survival of tubercle bacilli following their exposure to heat is described. This method should be applicable for studying the effects of heat on other microorganisms.

2. Human tubercle bacilli (both avirulent and virulent), planted on good nutrient media, will grow at 42°C. (107.6°F.) when all the other requirements for the growth of the bacilli, such as appropriate hydrogen-ion concentration, isotonicity, water and air-balance, and nutrient needs are preserved. This temperature is above that tolerable for any length of time by the human body.

3. The range of temperatures below 60°C., which previously had been inadequately studied, is included in this study. At 60°C., fine suspensions (1 mgm.) of human tubercle bacilli in a buffered isotonic solution of pH 7.0 were killed within a few minutes; while at 50°C. the bacilli survived for 5 hours; and at 45°C., they survived for 8 days. With smaller numbers of bacilli, the survival period was shortened. The heat-survival period of human tubercle bacilli follows a logarithmic curve in the important range from 60° to 50°C.

4. *In vivo* experiments with hyperpyrexia gave negative results, in that human tubercle bacilli could not be destroyed by heat *per se* at temperatures consistent with the integrity of the tissues.

We are grateful to Mr. L. D. Miller for assisting with the technical phases of this study, and to Mr. Murl G. Simpson for assisting with the radio-wave heat studies.

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STUDIES WITH BCG[1,2,3]

I. The Present Method of BCG Cultivation and Vaccine Production as Practised at the Pasteur Institute and the Tice Laboratories

SOL ROY ROSENTHAL

The method of culture of the bacillus of Calmette and Guérin has undergone many changes since its inception. Because there are ever-increasing reports demonstrating that this form of vaccination is safe and efficacious, and because, despite antagonistic reports, this method is gaining in popularity, this paper is offered to describe in detail the method employed and the cultural characteristics of *BCG*. This method is that employed at the Pasteur Institute now[4] as in 1934, when the author was an assistant under Dr. Guérin. To the knowledge of the writer, such a report is not yet found in the American literature.

The Tice Laboratories, a division of the Municipal Tuberculosis Sanitarium of Chicago, have for the past two years followed this procedure with but slight modifications.

SPECIAL APPARATUS

1: Roux tubes: These tubes are 1 inch in diameter and 8 inches long, having a $\frac{3}{16}$-inch constriction about 2 inches from the butt (see figure 3).

2: Spatula: The platinum spatula is 3 inches long, with a flat surface at its periphery, 1 inch long by $\frac{1}{4}$ inch wide, rivetted into a $\frac{3}{16}$ inch in diameter stem with holder 13 inches in length. The metal portion, including the spatula, measures $10\frac{1}{2}$ inches in length, while the holder measures 5 inches in length.

3: Potato bore: A $\frac{7}{8}$-inch inside diameter brass tube about 5 inches in length is beveled at one end to allow for a cutting edge. About one inch from the latter a window is cut, $2\frac{1}{4}$ inches long, bisecting the cylinder.

[1] From the Tice Laboratories, a detail of the Municipal Tuberculosis Sanitarium (Dr. Frederick Tice, President), Chicago, Illinois.

[2] From the University of Illinois Department of Bacteriology and Public Health (Dr. Lloyd Arnold).

[3] From the Illinois State Department of Public Health, Research Division (Dr. Lloyd Arnold).

[4] By personal communication with Dr. Guérin in 1936.

The end opposite the cutting one is stoppered with a rubber or wooden stopper.

4: Racks were so constructed to allow the Roux tubes to be held at a 15° angle.

5: Water-bath is of sufficient depth and capable of generating 75°C. constantly.

MEDIA

Glycerinated-water-potato: Cylinders of potatoes are cut, with potato bore, about 2 inches long and are bisected vertically. These slabs are placed in water, to which 10 gm. sodium carbonate has been added to each litre, for 2 hours. Following this procedure the potatoes are washed for two additional hours in running water. The latter are then dried on sterile towels and introduced into the Roux tubes, to which glycerinated (5 per cent) water has been added up to the point of constriction. The tubes are then plugged with a fairly tight-fitting cotton stopper that does not extend beyond the end of the tube. Sterilization in the upright position is carried out at 120° for 30 minutes. The tubes are allowed to cool and are then capped with rubber caps. Incubation for sterility is necessary for two days.

Glycerinated-bile-potato: Slabs of potato, as above, are washed for 2 hours in running water and then placed in glycerinated (5 per cent) beef-bile[5] and kept at 75° in a water-bath for two hours. The Roux tubes are then filled to $\frac{1}{4}$ inch below the point of constriction with the heated glycerinated bile, and the potatoes are then inserted. Cotton stoppers, sterilization, and capping are executed as above.

Sauton: This medium is used exclusively for *BCG* vaccine cultivation, and is composed of the following ingredients:

Asparagin	4.0 gm.
Citric acid	2.0 gm.
Potassium hypophosphate	0.5 gm.
Magnesium sulphate	0.5 gm.
Iron ammonium citrate	0.05 gm.
Water	940 cc.
Glycerine	60 cc.

After the asparagin and the salts have been well heated, the iron ammonium citrate is added and boiling is allowed to continue for one minute.

[5] The beef bile is obtained from the Stock Yards and is at once sterilized at 120°C. for one hour. It is kept at room temperature for at least three weeks and not over six months. An abundant copper-colored pigment settles, which is filtered through paper immediately before using.

Cooling must be complete before adjustment of the pH to 7.2 to 7.3 with pure ammonia. The solution in 150-cc. amounts is poured into 250-cc. Florence flasks, stoppered and capped with paper. Autoclaving at 120°C. is continued for one hour.

CULTURES

Two sets of cultures are supported so that one set may be transferred weekly. Each group is thus reinoculated every 2 weeks. Of each set there are two groups of tubes, one of glycerinated-water-potato, the other glycerinated-bile-potato. The former is used for the vaccine production while the latter is held for stock.

Glycerinated-water-potato cultures: Growth on the potato surface is seen after a few days, and it appears as varying-sized large granules up to 2 mm. in diameter. After a week's time these have increased in number and fused, so that a granular elevated coil covers the entire surface. At the end of the second week the coiling has become very dense, and growth may even extend upon the surface of the glass. On the fluid part of the media there appears, at the end of the first week, a flat, finely granular veil with only an occasional elevated granular coiled island. The islands increase until they almost replace the veil by the end of the second week.

A heaping spatula of growth from the potato is transferred upon similar media and ground upon the second surface until all the granules have been crushed. From the veil floating on the fluid part of the media loopfuls are transferred upon several flasks of Sauton, care being exercised to float these transplants.

The growth becomes dry and more granular after some five to ten subcultures upon glycerinated-water-potato, and the veil less luxuriant, with ever increasing islands at the expense of the intervening veil. The fluid itself becomes more and more amber tinted after numerous transplants. At this stage the medium should be changed to glycerinated-bile-potato for one or two generations, after which time a return to the glycerinated-water-potato can ensue. When using veils for Sauton, only those taken from glycerinated-water-potato medium at least twice removed from the bile should be employed.

Glycerinated-bile-potato cultures: Growth on bile is slower and less luxuriant than on other media. After the first week there is a diffuse large granular film covering a part of the potato surface. At the end of the second week the growth has spread diffusely and may measure up

to 2 mm. in thickness. The surface is flat but granular, rarely being smooth. Surface growth on the fluid does not take place. Transfers by means of the spatula are made as usual on similar media, but also on to glycerinated-water-potato.

The growth on the glycerinated-water-potato once removed from bile is very prolific and differs from similar cultures described above. At the end of the first week the entire surface is covered with a densely coiled, moist growth which extends on to the sides of the glass. The fluid surface veil is flat without island-formation, and here, too, growth extends well up on the glass of the tube. With age of the culture this veil becomes folded, but islands are rare. Subsequent reinoculations of the veil described yield an increased number of granular, coiled, elevated islands.

Sauton cultures: The first generation on Sauton from potato begins to develop after the first day: slowly at first, but after one week with increased rapidity, until by the tenth day the entire surface is covered by a flat, delicate veil with few or many folds and only an occasional elevated granular island. At this point subcultures on to other Sauton flasks are made. The latter growths differ from their mother culture in that the number of elevated islands increases at the expense of the intervening veil. One does not find the formation of a primary veil with secondary island-formation, but rather a concomitant development of islands and veil. With age (3 weeks) this subculture has grown markedly and is now characterized by dense, coiled loops, like loops of small intestine, reaching a surface-growth thickness of 4 to 5 mm. The colonies are yellow-gray in color, granular and moist. The fluid of the media remains clear and assumes an amber color. The pH concentration at this time (21 days) is slightly lower than heretofore, and the average pH equals 7. From the 25th to the 31st day it averages 6.2. By the 35th day the average pH equals 6. These results are from 90 flasks. Growth ceases after the 4th week, at which time small portions of the growth have sunk to the bottom. Cultures (21 to 30 days) are used in the preparation of the vaccine.

PREPARATION OF VACCINE

Special apparatus: 1: A specially constructed funnel with a 3-opening lid, obturator, and ramming rod. (See figure 1.) *2:* Pyrex glass ball mill, with $\frac{3}{8}$-inch stainless steel ball bearing. (See figure 2.) *3:* Rotary capable of developing 30 revolutions per minute. *4:* Metal funnel with perforated obturator and lid. *5:* Dispensing bottles.

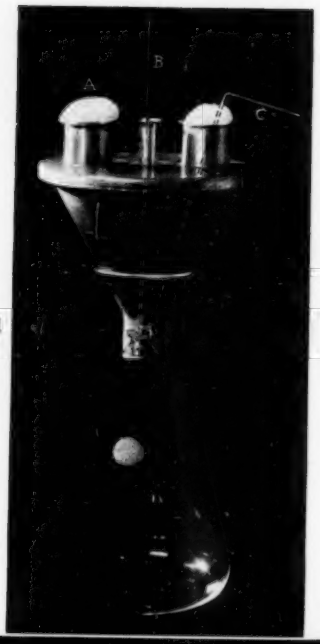


Fig. 1

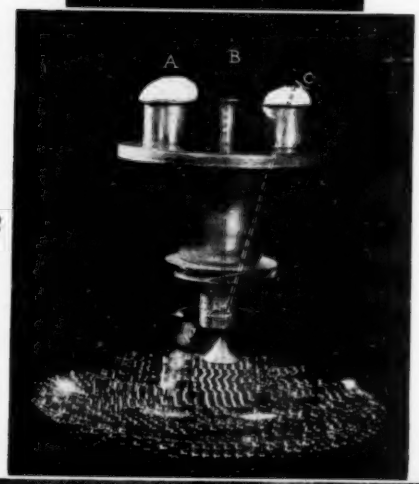


Fig. 2

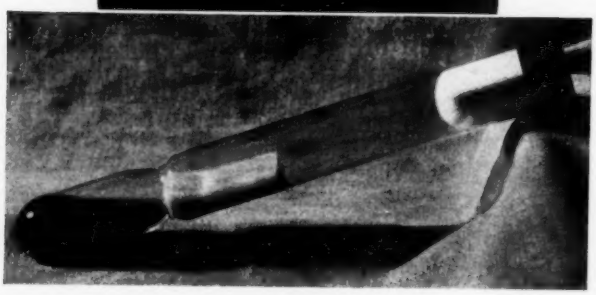


Fig. 3

Method: A culture of *BCG*, 21 to 30 days old, grown on Sauton at 38°C., usually weighs about 5 gm. The weighing is dispensed with, as numerous preliminary weights have established a fairly accurate, constant figure.

The mouth of the Sauton flask is flamed well, the flask shaken, and the contents poured into the free opening of the specially constructed funnel (A). (See figure 1.)

When the fluid is completely drained off, this funnel is transferred to the glass ball-mill and the obturator (B) disengaged, as seen in figure 2. By means of the rammer (C) the bacilli are loosened as much as possible, and finally 40 cc.[6] of water is poured into opening A to wash down the remaining bacilli.

The funnel is then removed, the ball-mill stoppered with a rubber stopper, and rotated by hand for a few seconds, until the large bacillary clumps are dispersed.

Fig. 1. Specially constructed funnel with opening (A), obturator (B), and rammer (C)

Fig. 2. Pyrex glass ball-mill with ½-inch stainless steel ball bearings. The obturator of the special funnel has been released.

Fig. 3. Photograph of Roux tube with potato and glycerinated bile. Note the contact of fluid with potato at constriction of glass.

Rotation for 10 minutes at 30 revolutions per minute is effected in the vertical position. When this is completed, 85 cc. of diluted Sauton (1 part Sauton to 3 parts of distilled water) is added to the mixture.

The metal funnel with perforated obturator is then placed in the dispensing flask, and 400 cc. of the Sauton is poured into the flask. The bacillary emulsion, as well as some of the steel balls, is poured into the funnel, and another 400 cc. of the diluted Sauton is poured over the steel balls.

The vaccine mixture thus prepared contains 5 mgm. of bacilli for each cc. of fluid (1 mgm. contains 40,000,000 bacilli). It is this dilution that is used for oral administration. For parenteral use dilutions can be made from the above mixture.

Tests for sterility and virulence: After rotating the bacilli emulsion and adding the first flask of diluted Sauton, a sample is taken by means of a Pasteur pipette and inoculated into broth and agar. Similarly, after the vaccine has been placed into vials, one of the latter is taken at random and cultured.

[6] All figures to follow for fluid are given per 5 gm. of moist weight of culture.

Each new culture used for vaccine production is tested for virulence by inoculating three guinea pigs intraperitoneally with 1, 5 and 10 mgm. of *BCG*. The method followed at the Tice Laboratories is the inoculation from the 10-day-old first generation on Sauton, so that, when the vaccine is ready for use, 31 to 40 days have elapsed and the animals can be examined.

DOSAGE

Oral: Two cc. or 10 mgm. are given in milk on the 5th, 7th, and 9th day after birth, making a total of 30 mgm.

Subcutaneous: 0.01 to 0.04 mgm. is injected in the scapular region of the back within the first week of life (1 cc. of the original vaccine is diluted with 100 cc. of diluted Sauton).

Intracutaneous: 0.01 to 0.1 mgm. is injected in the skin of the outer aspects of the thighs (1 cc. of the original vaccine is diluted with 10 cc. of diluted Sauton).

Scarification: This method was developed at the Tice Laboratories, and consists of shaving the skin and applying one drop of the concentrated vaccine thereon. A needle held tangentially to the skin is thrust upon the latter through the drop of vaccine with enough force so that the point of the needle punctures the horny layers of the epidermis. Thirty such strokes are made. In guinea pigs the tuberculin test becomes positive after 7 days. (Following the intracutaneous method given above, the test is positive only after 2 to 3 weeks.)

STUDIES WITH BCG[1,2,3]

II. Attempts at Dissociation and Increase of Virulence

SOL ROY ROSENTHAL

The opponents of Calmette and Guérin's method of vaccination believe that a return to virulence of the organism can occur. These antagonists may be divided into three groups:

1: Those who believe that *BCG* grown according to the methods of Calmette and Guérin, may develop in animals a slowly progressive and, at times, a fatal tuberculosis.
2: Those who believe that the virulence of *BCG* can be enhanced by animal passage.
3: Those who believe that microbic dissociation may occur as noted by the virulent S forms, or that by special methods of culture an increase of virulence may be effected.

To this host of antagonists, protagonists of even larger numbers have arisen to disprove that augmentation of *BCG* virulence occurs. The latter group, which will be mentioned in greater detail below, is increasing in number as the former is decreasing. If general agreement as to the stability of *BCG* can be established, a stride forward in the control of tuberculosis will have been made, for since the discovery of the tubercle bacillus it has been conceded that immunity against tuberculosis can only be accomplished by the presence in the host of viable tubercle bacilli. *BCG* up to the present time has met, better than any other form of tuberculosis vaccination, the requirements of immunization. It is avirulent and produces tubercles in the body as well as positive skin reactions to Old Tuberculin.

This work endeavors to repeat some of the important contributions in each of the groups mentioned above. Many interesting incidental findings have also resulted from this study.

[1] From the Tice Laboratories, a detail of the Municipal Tuberculosis Sanitarium (Dr. Frederick Tice, President), Chicago, Illinois.
[2] From the University of Illinois Department of Bacteriology and Public Health (Dr. Lloyd Arnold).
[3] From the Illinois State Department of Public Health, Research Division (Dr. Lloyd Arnold).

1. ANIMAL INOCULATIONS OF BCG TAKEN FROM STANDARD MEDIA AS DESCRIBED BY CALMETTE AND GUÉRIN

Petroff reported that in a large group of animals inoculated with *BCG* a small number developed a progressive type of tuberculosis. It was this observation that led him to the idea that there must be a virulent and avirulent form of the organism. Repetitions of this work have not been

TABLE 1

Observations in animals inoculated with BCG

ROUTE OF ADMINISTRATION	NUMBER OF ANIMALS	DOSE IN MGM.	REACTION WITH TUBERCULIN	GROSS PATHOLOGY	
				Within 3 weeks	After 3 weeks
			per cent		
Intracardial.....	17	10 to 20	100	Miliary tubercles in liver, lung, spleen, and kidney	None
Intraperitoneal.....	42	10 to 15	83	Rolling of omentum with tubercles of same. Tubercles on surface of liver and spleen	Slight fibrosis of omentum
Intracutaneous.....	27	10	100	Local abscess with surrounding specific reaction. Local lymph nodes enlarged	Small scar at site of inoculation
Subcutaneous.....	11	10 to 15	100	As above and extension into muscle	Minute scar at site of inoculation
Oral.....	18	20 to 30	0	Swelling of mesenteric lymph nodes	None

Note: An additional 200 animals (guinea pigs and rabbits) used for other experimental purposes but inoculated with large doses of *BCG* showed no evidences of progressive tuberculosis.

numerous (Korschun, Watson, McIntosh, Konst, Chiari, Nobel and Sole). Those who did not find a progressive tuberculosis developing in animals inoculated with *BCG* are many (Calmette and Guérin, Boquet, Nègre, Valtis, Griffith, Gerlach, Kraus, Neufeld, Park, Chiari, Coulaud, etc., etc.).

The cultures used in this study were obtained by the author from Dr. Guérin at the Pasteur Institute. They are now in their 524th generation,

having been in this laboratory for 93 generations. Animals were inoculated at regular intervals from different generations. Varying routes of administration were used. Table 1 briefly summarizes the results.

In table 1, 115 animals (guinea pigs) were inoculated as indicated. In no instance was a progressive tuberculosis noted. The animals were killed at varying intervals but adequate numbers in each group were allowed to live for periods of over a year. In addition to the animals mentioned above, there were about 200 more (guinea pigs and rabbits) used for other experiments that had received large doses of *BCG*. The results were similar to that mentioned above.

More detailed macroscopic and microscopic observations will be reported in another publication. It is sufficient to note here that after intracardial inoculation of the *BCG*, the tubercles that formed in the lung, liver, spleen and kidneys never reached more than miliary size, and regression began after the second to third week. After one to two months, tubercles were rare. Lymph-node enlargements sometimes remained over a long period, but this was not constant.

The intracutaneous and subcutaneous inoculations resulted in local abscess-formations with spreading into the muscular tissue and local lymph-node swelling. Evacuation of the abscess or resorption began after the first week, and by the second to fourth week small scars were already evident. Specific tuberculous changes about the abscess were always found. Following intraperitoneal inoculation, there was a rolling up of the omentum with tubercle or small abscess-formations. Swelling of the omental lymph nodules as well as the peritracheal lymph nodes occurred. Except for minute scars in the omentum, restitution was established after one to two months.

For the oral group, young guinea pigs not over one week old were fed by means of a dropper on three successive days. Mesenteric lymph-node enlargements were the only evidences of reactivity seen grossly. The latter regressed after one month.

Summary: *BCG*, cultivated according to the methods recommended by Calmette and Guérin, calls forth, when injected into the animal body, the formation of tubercles and a skin sensitivity to Old Tuberculin. When administered orally, *BCG* does not produce the above. In a series of 115 guinea pigs and an additional 200 animals (guinea pigs and rabbits) progressive tuberculosis did not occur when *BCG* was injected in large doses by varying routes.

2. PASSAGE OF BCG THROUGH A SERIES OF ANIMALS

Korschun, Petroff, Branch and Steenken, Nobel and Sole, and Watson report an increase of *BCG* virulence by animal passage. Kirschner was able to make six successful reinoculations without an increase of virulence. However, Kraus, Uhlenhuth, Gerlach, Berger, Lange and Glauberg, Silberschmidt, Birkhaug, Behner, etc., etc., were unable to successfully reinoculate animals beyond the second to the fourth generation. The latter authors did not find an augmentation of virulence by this procedure.

Evidently avirulent tubercle bacilli cannot be enhanced in their virulence by animal passage. Willis, using R1, was unable to increase its virulence after 110 passages through guinea pigs, using a thousand of these animals.

Guinea pigs were inoculated intracardially, subcutaneously, intracutaneously, and orally with 10 to 30 mgm. *BCG*. After varying intervals of time (see tables 2, a, b, c, d), the guinea pigs were killed, and the lungs, liver, spleen, enlarged lymph nodes, and any suspicious organic lesion were removed and ground fine with sterile sand. A 5 per cent solution of sulphuric acid was added (about 5 cc. to each gram) to the organs and the mixture was allowed to stand for 10 to 30 minutes. The latter was centrifugated, washed with saline solution, and the same procedure repeated for three operations. (The reaction was neutral to litmus paper at this point.) The sediment was then inoculated intraperitoneally into guinea pigs and also seeded on Loewenstein's egg medium (pH 7). A similar procedure was followed for the subsequent series of animals. The organs of animals of one group in the latter series were pooled. When abscess formed, as with the intracutaneous and subcutaneous groups, these lesions were not included in the inoculation.

The purpose of the experiment, namely, to increase the virulence of the organism, was not accomplished. Indeed, after the first series of animals, specific lesions were exceedingly rare. Lymph-node enlargements, especially of the posterior tracheal group, were frequent but not constant.

Many incidental findings occurred, which are of interest and are recorded in tables 2a, b, c, d. Table 2a reveals very strikingly that sensitivity to Old Tuberculin (0.2 cc. of a 1:10 solution) did not appear until the first month, but that smears and cultures of the organs, as well as pathological changes, were positive for tuberculosis during this period. With the appearance of skin sensitivity, positive smears or cultures were

TABLE 2a

Observations following intracardiac injection of BCG and subsequent intraperitoneal inoculations of organs

1st inoculation: guinea pig number	2nd inoculation: guinea pig number	3rd inoculation: guinea pig number	4th inoculation: guinea pig number	Time killed after inoculation	Tuberculin reaction	Postmortem smear of organs	Postmortem culture of organs	Postmortem findings
				days				
12				8	−	+	+	Tubercle over pericardium; miliary nodules in left kidney
	27			72	−	−	−	Negative
	28			72	−	−	−	Negative
3				14	−	+	+	Tubercles over pericardium and lung
	13			40	−	−	−	Negative
	15			40	−	−	−	Negative
		42		90	−	−	−	Negative
		48		90	−	−	−	Negative
			66	130	−	−	+	Negative
			61	130	−	−	+	Negative
7				15	−	+	+	Tubercles in lung and kidney
	20			56	−	−	−	Negative
	24			56	−	−	−	Negative
		235		54	−	−	−	Negative
		247		54	−	−	−	Negative
1				24	−	+	+	Nodules over pericardium and tubercle in kidney
	32			64	+	−	−	Negative
	37			64	+	−	−	Negative
6				25	−	+	+	Nodules over pericardium
	26			72	−	−	−	Negative
	29			72	−	−	−	Negative
9				26	−	+	+	Nodules over pericardium; miliary nodules in liver and kidney
	31			64	−	−	−	Negative
	34			64	+	−	−	Negative
18				50	+	−	−	Negative
	238			64	−	−	−	Negative
	240			64	−	−	−	Negative
		51		150	−	−	−	Negative
		62		150	+	−	−	Negative
			198	210	+	−	−	Negative
			200	210	+	−	−	Negative

TABLE 2a—*Concluded*

1ST INOCULATION: GUINEA PIG NUMBER	2ND INOCULATION: GUINEA PIG NUMBER	3RD INOCULATION: GUINEA PIG NUMBER	4TH INOCULATION: GUINEA PIG NUMBER	TIME KILLED AFTER INOCULATION	TUBERCULIN REACTION	POSTMORTEM SMEAR OF ORGANS	POSTMORTEM CULTURE OF ORGANS	POSTMORTEM FINDINGS
				days				
22				69	+	−	−	Scar at site of inoculation of pericardium
	229			76	−	−	−	Negative
	246			76	−	−	−	Negative
8				70	+	−	−	Negative
	148			51	−	−	−	Negative
	149			51	−	−	−	Negative
		56		195	−	−	+	Negative
		53		195	+	−	−	Negative

TABLE 2b

Observations following intracutaneous injection of BCG and subsequent intraperitoneal inoculations of organs

1ST INOCULATION: GUINEA PIG NUMBER	2ND INOCULATION: GUINEA PIG NUMBER	TIME KILLED AFTER INOCULATION	TUBERCULIN TEST	POSTMORTEM SMEAR OF LOCAL LESIONS	POSTMORTEM SMEAR OF ORGANS	POSTMORTEM CULTURE OF ORGANS	GROSS PATHOLOGY
		days					
128		14	+	+	−	−	Indurated local lesion and enlarged lymph node
	236	52	−	−	−	−	Negative
	242	52	−	−	−	−	Negative
134		27	+	−	−	−	Local 3-mm. scar, local lymph node enlarged
	243	76	−		−	−	Negative
	244	76	−		−	−	Negative
145		73	+	−	−	−	Negative
	60	232	+			−	Negative
	54	232	+			−	Negative

TABLE 2c

Observations following subcutaneous injections of BCG and subsequent intraperitoneal inoculations of organs

1st inoculation: guinea pig number	2nd inoculation: guinea pig number	Time killed after inoculation	Tuberculin test	Postmortem smear of local lesions	Postmortem smear of organs	Postmortem culture of organs	Gross pathology
		days					
82		1		+	−	−	Local hyperaemia and pus cells; lymph node hyperaemia
	95	90	−		−	−	Negative
94		8	−	+	−	−	Local abscess and enlarged lymph nodes
	81	180	−			−	Negative
	88	180	−			−	Negative
68		50	+	−	−	−	Small scar at site of inoculation
	89	150	−			+	Negative
	90	150	−			+	Negative
93		95	+	−	−	−	Negative
	191	216	+	−		−	Negative

TABLE 2d

Observations following oral administration of BCG and subsequent inoculations of organs

1st inoculation: guinea pig number	2nd inoculation: guinea pig number	3rd inoculation: guinea pig number	Time killed	Tuberculin test	Postmortem smear	Postmortem cultures	Gross pathology
			days				
308			6	−	−	−	Enlarged mesenteric lymph nodes
	55		154	−	−	−	Hilum of lung, lymph nodes slightly enlarged
	57		154	−	−	−	Hilum of lung, lymph nodes slightly enlarged
312			15	−	−	−	Slightly enlarged mesenteric lymph nodes
	58		94	+	−	−	Hilum of lung, lymph nodes slightly enlarged
	63		94	+	−	−	Hilum of lung, lymph nodes slightly enlarged
		178	210	−	−	−	Negative
		187	210	−	−	−	Negative
309			27	−	−	−	Negative
	67		90	−	−	−	Negative
	72		90	+	−	−	Negative
304			90	−	−	−	Negative
	83		90	−	−	−	Negative
	84		90	−	−	−	Negative

not found, nor were specific evidences of tuberculosis seen grossly. In 7 animals, positive tuberculin tests followed in the second, third, or fourth series of inoculations of organs of infected animals, although the organ cultures in these cases were negative. In three cases positive cultures for *BCG* were obtained, but the tuberculin tests remained negative (killed after 130 to 195 days). In one animal (no. 56) that had received the same organs as were inoculated into one of the three animals above mentioned (no. 53), the tuberculin skin test was positive while the cultures of the organs were negative.

The interpretations of the above findings are numerous: (1) that with the appearance of allergy the tubercle bacilli are destroyed (Lurie); this is only partially true in that it does not explain the positive organ cultures of guinea pig no. 56 (see also guinea pigs no. 89 and 90 in the subcutaneous series); (2) that substances are found in the lung, liver, spleen, lymph nodes when allergy sets in that inhibit bacillary growth; (3) that not sufficient or the same tissue could be used for inoculating both the culture media and the guinea pigs; (4) that granular or submicroscopic forms may be present, and only after many reinoculations in animals can tubercle bacilli be recovered (animals nos. 61, 66, and 56). The latter view corresponds to those of Calmette, Nègre, Boquet, and the entire French school.

In tables 2b and c, results similar to those of the intravenous group were noted. Animals 89 and 90 (table 2c) gave positive *BCG* cultures of their organs despite the fact that the organs with which they were inoculated (no. 68) yielded negative cultures. The tuberculin test in no. 68 was positive. Is it possible that the *BCG* had become so innocuous that it remained in the animal host without setting up an allergic reaction, or are some animals more refractory to *BCG* than others? Finally, are we dealing with submicroscopic forms of tubercle bacilli?

The oral group (table 2d) presents results which are equally difficult to explain. In no instance were positive cultures or tuberculin reactions noted when *BCG* was given by mouth (18 young guinea pigs were so treated). Yet in three animals that received the organs of the above intraperitoneally, positive tuberculin skin tests were noted. Cultures of the organs of the animals subsequently remained negative. Again the question of submicroscopic forms presents itself.

Summary: Passage of *BCG* through a series of animals did not enhance its virulence. On the contrary, a decrease in the virulence was the rule.

Interesting incidental findings were that with the appearance of skin

sensitivity to Old Tuberculin, *BCG* could not be recovered from the organs of such animals upon culture. Specific gross tuberculous changes also disappeared with skin sensitivity. This observation again stresses the importance of allergy and immunity. It is not the subject of this paper to discuss their relationship, but, using an avirulent tubercle bacillus in the methods and doses above described, the appearance of allergy coincides with the disappearance of directly culturable organisms (see cultures in series). Their relationship must be more than casual.

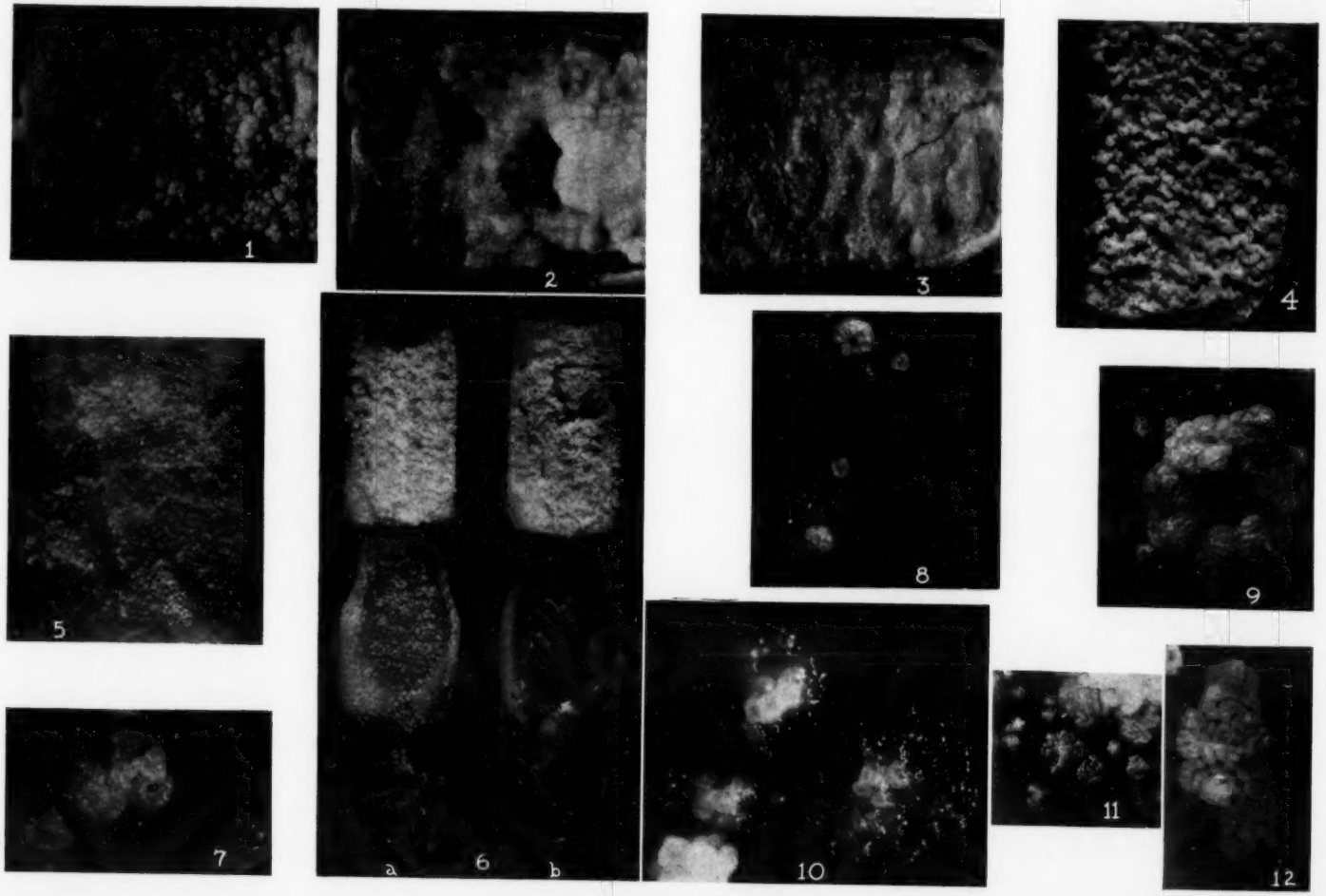
That bacillary constituents were present in some form, even in allergic animals, must be conceded, for they could occasionally be recovered after animal inoculations in series. Because in one series, recovery of tubercle bacilli did not take place until the third reinoculation and in two other cases until the fourth reinoculation (the intervening animals gave negative organ cultures as well as skin-sensitivity tests), the question of submicroscopic forms must be seriously considered. According to the views of Fontes, Calmette, Nègre, Boquet, and the entire French school, filterable forms may be recovered in their original acid-fast bacillary state only after repeated inoculations of animals in series. They believe that they have demonstrated the cycle of the bacillus *in vivo*, as Kahn, Mellon, Lindgren, Enderlein and others have done *in vitro*.

The oral administration of *BCG* did not yield positive organ cultures or skin tests, yet upon inoculating the organs of the latter in fresh animals positive tuberculin tests were at times called forth. This observation again stresses the submicroscopic bacillary forms.

3. BCG DISSOCIATION

The work on dissociation of tubercle bacilli, including *BCG*, by Petroff, Steenken, Branch and Oatway, is well known (also Seiffert, Much, Begbie, etc.). Following the method of selection and pH variation as used by these authors, many other methods for *BCG* dissociation and tubercle bacilli generally have arisen: Anti-R serum (10 per cent) in fluid media; alkaline basic fluid media; ferric chloride (0.0004 per cent) added to egg media; passage through animals and continuing by colony selection and pH variation, etc. Others have reported that certain media increase the virulence of *BCG* without stressing the colony morphology:—deep seeding in infusion bouillon enriched with Witte's peptone (Dreyer and Vollum), the use of normal rabbit serum (10 per cent) in Sauton, etc.

If, in the sense of Petroff, dissociation of *BCG* means that the mutant



Figs. 1 to 12

S has virulent properties, then a large host of workers has refuted all of the above results (Calmette and his co-workers, Guérin, Nègre, Boquet and Birkhaug, Gerlach, Brosch and Kaplan, Kraus, Lange, Park and Mishulow, Meissner and Prausnitz, Shaffer, Sulmann, Behner, etc.).

As repetition of the above work in the United States was deemed advisable, the following is offered:

Solid media: 1: Colony selection with variation of the pH media: colonies were picked from potato media or from flat veils of the fluid part

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Fig. 1. Surface growth on glycerinated potato-bile, two generations removed from glycerinated water potato-bile. Age of culture, 1 month. Note the large granules.

Fig. 2. Surface growth on potato-bile continuously on the same medium. Age of culture, 21 days. Note the fusing of granules.

Fig. 3. Surface growth on glycerinated potato-bile, grown with a tightly fitting rubber stopper. Age of culture, 1½ years. Compare with fig. 1 for smoothness of surface.

Fig. 4. Surface growth on glycerinated water potato. Age of culture, 15 days. Note the coiled surface, which is the normal type of growth.

Fig. 5. Surface growth on water potato after applying the tightly fitting rubber stopper. Age of culture, 1½ years. Note the small and large granules, and the flat appearance of the growth.

Fig. 6. Roux tubes, showing surface growths on glycerinated water potato, as well as on the surface of the fluid in the butt. Age of culture, 15 days. In 6a the small islands of growth on the fluid are numerous, while in 6b no such islands occur but rather a smooth veil with ridges. The potato surface growths are similar. Tube 6a is twice removed from potato-bile, while 6b is only once removed.

Figs. 7 & 8. Colonies on Loewenstein's malachite-green egg medium (pH 6.1). This is the 12th generation from an original blood-culture. Age of colony, 5 days. Note the single large granular colonies, the coiled and the crater-like ones composed of similar granules. The demarcation of colony and medium is distinct.

Fig. 9. Giant crater-like colonies. Age of culture, 57 days.

Fig. 10. Colonies with edges sloping into the medium (pH 7.2). These colonies were found in the butt of the tube where much moisture was present. Age of culture, 20 days. Source, organs of infected animals.

Fig. 11. Colonies with sloping edges near mouth of tube where considerable drying has taken place. Age of colony, 2 months. (pH 7.2.)

Fig. 12. Coiled colonies, grown at junction of medium and glass. Note that about one-half of the colony has extended upon the surface of the glass, and that this portion is veil-like and flat. Age of colony, 26 days.

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of the potato media or Sauton (10 days to several months old), mixed with a few cubic centimetres of salt solution (pH 7.8), filtered through a Whatman's no. 5 filter, and the filtrate inoculated on Loewenstein's malachite-green egg medium adjusted to a pH of 6.5 and 7.8. Later in the study the pH's of 6.1 and 7.2 were also used. Subcultures were made

by colony selection and filtration as above. Both Kolle flasks and tubes were employed. (Method of Petroff.)

2: Same as above, using cultures derived from blood or organs of animals inoculated intracardially with *BCG.*

3: Same as in 1, using cultures derived from lymph nodes after direct inoculation in same medium. (Method of Ninni.)

4: Addition of 0.0004 per cent ferric chloride to Loewenstein's egg medium adjusted to a pH of 7.2. (Method of Alexander.)

Fluid media: 1: Cultivation of *BCG* on Sauton, to which 10 per cent anti-R rabbit's serum had been added. (Method of Petroff.)

2: Cultivation of *BCG* as above, using 10 per cent normal rabbit's serum. (Method of Sasano and Medlar.)

3: Cultivation on Sauton adjusted to a pH of 7.8. (Modified method of Reed, Orr and Rice.)

Results on solid media: The colony morphology in most respects was similar and thus, notwithstanding the source of the culture, this group will be discussed as one.

As a rule, the first cultures isolated from lymph nodes, organs, or blood showed the greatest colony variation. This was equally true when the type of medium was changed. With subsequent selection, filtration, and seeding, a more or less uniform picture was observed. Optimum growth of the organisms occurred at a pH of 6.1 and 6.5. At a pH of 7.2 growth was less luxuriant, but a greater amount of variation was seen. Moderate to no growth occurred when the medium was adjusted to a pH of 7.8.

The studies here described have been carried out over a period of two years. It was not found necessary to extend the cultures in this series beyond their 15th generation.

Two large groups of colonies could be distinguished:

1: The large granular colonies (90 to 99 per cent): These colonies began as pinpoint to pinhead-sized spherical granules, butter-colored, with a smooth, glossy surface. The latter developed into many different forms,—coil-like, crater-like, or simply by enlargement of the original granule. In every case the unit of the colony, as seen by magnification, was found to be a large granule (figures 7 & 8). The relationship of the surface of the medium to the colonies was well demarcated except in some cases, especially of the enlarged single granular type, when a secondary, finely granular veil extended as a halo about the colony and into

the medium. With age (6 weeks or more), this smooth veil was usually found to be replaced by a coiled, elevated superstructure. When this did not occur, subcultures of the veil alone yielded the typical large granular colonies. Cultures, six weeks or older, revealed that the surfaces of the large granules became finely granular. Chromogenicity (orange to light brown) of isolated colonies occurred with age, but subcultures of the latter yielded the usual butter-colored colonies.

2: The finely granular colonies (1 to 10 per cent): This unit of structure was pinpoint-sized, and at times could be seen only by use of a hand lens. The color was somewhat paler than above and the surface was smooth. Two types of colonies were noted,—plateau-like with bevelled edges sloping into the medium, or a veil-like structure with elevated central ridges radiating from an indefinite centre into the medium. The veil-like structures described usually developed at the junction of medium and the glass, and it was not uncommon to see more than half of the veil growing upon the glass itself (figure 12). Another favorite location was near the butt of the tube, where much moisture had accumulated, or near the mouth where drying was more rapid (figures 10 & 11). Exclusion of air also favored the development of these colonies. Subcultures of these individual colonies by the method above mentioned gave the usual colony differences. In one instance in which the source was a blood culture, the proportion of this type of colony reached 30 per cent in the 12th generation, but reversion to the usual proportions soon transpired. Rarely, a finely granular growth became superimposed upon a roughly granular one.

Whenever suspicious smooth colonies developed, guinea pigs were inoculated. There were 25 animals thus subjected. In no case was there any evidence of progressive tuberculosis. Suspension in salt solution of pH 7.8 of both types of colonies was facilitated with moderate ease.

Summarizing: Variations in colony morphology do occur and are dependent upon the media in which *BCG* is grown, pH concentration, drying, moisture, lack of oxygen, contact with glass, etc. These changes are transitory and reversion to the usual form occurs after one or more subcultures. Animals inoculated with suspicious colonies of the finely granular type did not develop progressive tuberculosis, or even more extensive lesions than the large granular types.

Results on fluid media: By growing *BCG* on Sauton, to which 10 per cent anti-R serum is added, Petroff claims to have recovered an S variant

which was pathogenic for laboratory animals. Sasano and Medlar reported increased virulence of *BCG* when grown on Sauton solution, to which 10 per cent normal rabbit's serum had been added (after the third generation). Reed, Orr and Rice report augmentation of virulence when cultivated on Proskauer and Beck's basic alkaline medium. It is of interest that the latter authors, when using the strain received from Paris, were unable to repeat this work after five years of study. Failure of verification of the above results is also reported by Boquet and Nègre, Park and Mishulow, Shaffer, Meissner and Prausnitz and others (see also literature by Irvine).

Three procedures were followed in this work:

1: Immune serum of rabbits (10 per cent) plus Sauton: To produce immune serum, rabbits were injected intracardially and subcutaneously for 4 to 5 injections with 10 to 20 mgm. of *BCG* at each injection. One week after the last injection the serum was tested for complement-fixing bodies by using Boquet and Nègre antigen "methylique" or the rabbits were tuberculin-tested, using the intravenous or intracutaneous methods. Usually one test or the other was positive at this time. Otherwise, another series of injections was given. This immune serum was added in 10 per cent amounts to Sauton adjusted to a pH of 7.2. (When the pH used was 7.8, growth of the organisms did not ensue.) Transfers were made when adequate growth had occurred, usually every two to four weeks.

The average results are recorded in table 3. It will be noted that two outstanding features are worthy of emphasis: First, that the first transfer of this media yielded a profuse growth of a delicate veil, which was granular on close inspection. Elevated colonies were few at first, but upon subsequent transfer or with aging of the culture the percentage of the latter increased, at the expense of the flat veil. Second, after the 3rd or 4th subculture there appeared the usual elevated coiled colonies, which sank to the bottom of the flask, but after one or even three months a secondary growth would appear on the surface of the fluid and growth would follow rapidly thereafter. This occurred on several occasions, and was rare for any other type of fluid medium. Subcultures of this secondary growth by the filtration method on solid egg media yielded the usual type of colonies. Growth did not occur on media adjusted to a pH of 7.8. Animal inoculations of similar flat colonies showed no increased virulence.

The bacterial morphology is of interest and shows variations corre-

TABLE 3

Observations of BCG growth on Sauton plus anti-R rabbit's serum

GENERATION NUMBER	SAUTON PLUS 10 PER CENT IMMUNE RABBIT'S SERUM	LOEWENSTEIN'S EGG MEDIUM	BACTERIAL MORPHOLOGY	REMARKS
1	Profuse growth of fine veil with few elevated colonies		Long, slender, granular acid-fast bacilli with many acid-negative granules	With age of culture elevated colonies increased
2	Profuse growth of fine veil with many elevated colonies	pH 6.5—R pH 7.8—no growth	As above	As above
3	Profuse growth of elevated coiled colonies. This sank and *secondary delicate* veil appeared on surface	Secondary growth pH 6.5—R pH 7.8—no growth	Secondary growth shorter and plumper bacilli; granular and all acid-fast	Injected second growth. Guinea pigs (3) showed no gross lesions 2 to 7 months after inoculation. (Tuberculin +.)
4	From secondary growth: moderate growth of veil and elevated colonies of equal dimensions	pH 6.5—R pH 7.8—no growth		With age of culture, increasing elevated coils
5	Moderate growth of coiled elevated colonies with intervening fine veil			
6	Growth at first slow of elevated coils; then after 3 weeks rapid, forming veil (4 days)	pH 6.5—moderate R pH 7.8—no growth	Large coarsely granular acid-fast bacilli; 20 per cent of granules acid-negative	
7	Profuse growth of veil with many ridges			Later 50 per cent of surface composed of elevated coiled colonies
8	Profuse growth of veil with many ridges	pH 6.5—R pH 7.8—no growth	Short, slender and granular; all acid-fast	As above
9	Slight growth, worm-like and flat; covers a 2-sq. cm. area	pH 6.5—R pH 7.8—no growth	Only occasional bacilli; much debris	Guinea pigs (2). No evidences of tuberculosis after 6 months. (Tuberculin +.)
10	No growth	pH 6.5—no growth pH 7.8—no growth	All debris	

sponding to the type and speed of growth. The first generation yielded the normal type of bacilli, long, slender, and granular, with many acid-negative granules. Subsequent transfers, especially if growth was at first retarded, yielded bacilli that were shorter and plumper. In the sixth generation the bacilli found were large and coarsely granular. When the normal profuse growth was retained, the original slender bacilli were again found. There appears then to be a cycle in both the growth characteristics of the organisms as well as in their morphology. This is not so much dependent upon the number of generations or the actual age of the transplant, as variations in the same culture could be found. The delicate veil, for example, yielded granular forms, whereas the elevated colonies yielded large plump bacilli. The fully formed veil presented the normal slender bacilli of the original culture. It must be borne in mind that the actual age of the transplant is not synonymous with the age of the bacillary growth.

2: Sauton plus 10 per cent normal rabbit's serum: Growth progressed rapidly of a coarsely granular ridged type of colony covering the entire surface of the Sauton (adjusted to a pH of 7.0) by the 10th day. Subcultures yielded similar and equally profuse growths on similar media up to the 5th generation when growth was retarded. Colonies were picked after the 3rd, 4th, and 5th generation, suspended in salt solution (pH 7.8), filtered through a Whatman's No. 5 paper, and inoculated on Loewenstein's medium of pH 6.1, 7.2, and 7.8. This yielded the usual results of coarsely granular colonies, with an occasional finely granular one on the two former types of medium, and slight to no growth on the latter medium.

Animal inoculations of colonies in their 3rd, 4th, and 5th generations (18 animals) did not result in the development of progressive tuberculosis.

3: Sauton adjusted to pH 7.8: The mother cultures here employed were the flat veils from the fluid part of the glycerinated-potato medium or similar veils on Sauton (10 days old). Such transfers on Sauton of pH 7.2 yielded very luxuriant growth, yet on Sauton of pH 7.8 growth was only initiated with great difficulty. When growth did occur, it would usually be moderate for the second to the third generation and then gradually stop developing. Occasionally, more profuse growths did occur, but these colonies would be elevated and coarsely granulated with but little veil, and could be subcultured as far as the fourth to fifth generation. Then, again, retardation of development was noted. By the seventh generation growth usually ceased. Subcultures on solid media,

suspended in salt solution of pH 7.8, filtering through Whatman No. 5 paper and seeding on Loewenstein's malachite-green egg media of pH 7.8, 7.2, and 6.1, yielded the usual variations of *BCG* colonies on media of low pH concentration.

COMMENT

Reports of *BCG* dissociation have become less numerous since 1928 and 1929; and, indeed, Reed, Orr and Rice, who had no difficulty in dissociating the *BCG* strain from the Trudeau Sanatorium (Petroff), Ottawa strain (Watson), Alberta strain (Rankin), and Montreal strain (Parizlau), were unable to show mutation of the Paris strain received directly from the Pasteur Institute after 5 years of study (1929 to 1934). Petroff, by personal communication with the author, admitted that the present strain is probably a pure R one.

The author received his cultures from Dr. Guérin at the Pasteur Institute in the early part of 1934. Changes in colony morphology did occur regularly, even by the use of the accepted media such as glycerinated-bile-potato or glycerinated-water-potato. Thus the first transfer from bile-potato on to water-potato yielded on the surface of the fluid a delicate veil, simulating the so-called S type of growth (figure 6b). By the next generation (figure 6a), the typical elevated granular colonies developed. The potato surface growths also varied with age of culture (figure 2), or if a sufficient amount of air was not present as by the use of a tight-fitting rubber stopper (figures 3 & 5). These forms were only transitory, and restitution to the normal morphology was easily facilitated (figures 1 & 4).

By the use of other methods, as described in the text that supposedly favor complete dissociation, it was noted that two types of colonies actually develop, the unit structure being large and small granules respectively. The former was dominant to the extent of 90 to 99 per cent. These formed coiled or crater-like colonies, while the small granular type formed sloping colonies, whose edges were intimate with the media (the so-called S type of the literature). The latter type of growth was more readily seen when an abrupt change in the type of the medium used was brought about,—changes in the pH concentration, drying, excessive moisture, insufficient air supply, etc. Reversion to the large granular type was prompt, and animal inoculations did not yield progressive tuberculosis or more extensive lesions than with the R type of colony. On the basis of animal inoculation, then, dissociation of *BCG* in the sense of increased virulence did not occur. Changes in colony

morphology did transpire, but more or less transitorily, probably associated with an arrest or acceleration of growth of the organism.

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STUDIES WITH BCG[1,2,3]

III A. The Effect of Phospholipins of BCG and Egg-Lecithin on BCG
III B. The Effect of Cholesterol or Lecithin Dissolved in Olive Oil on BCG

SOL ROY ROSENTHAL

A. THE EFFECT OF PHOSPHOLIPINS OF BCG AND EGG-LECITHIN ON THE BACILLUS OF CALMETTE AND GUÉRIN

The chemistry of the tubercle bacillus has been studied in great detail by both the American and the French schools. Their work indicates that of the three fractions of the organisms, namely, the protein, the fat, and the carbohydrate, the first two are the most important. The protein fraction is antigenic (Seibert); and produces skin sensitivity but no specific histological tissue response. The acetone-insoluble but alcohol- and ether-soluble fat fraction (the saponifiable, dextrorotatory, phthioic-acid portion of the phospholipins (Macheboeuf, Anderson)) is haptogenic and calls forth the epithelioid reaction of the host (Sabin, Doan, Forkner), similar to that produced by the bacillus itself. The status of the polysaccharide is less known, but is supposedly toxic and can produce anaphylaxis (Sabin, Doan and Forkner).

Although the entire rôle of the phospholipins is still not completely understood, it is agreed by most authors that these substances have to do with the specific immunity in tuberculosis as well as the specific tissue response.

Can the phospholipin content of the tubercle bacillus be increased by growing the latter on a medium containing lecithin? It appears that, when large concentrations (5 to 10 per cent) of lecithin are used in the medium upon which these organisms are grown, a bacteriolysis occurs with loss of acid-resistance of the organisms (Platonov, Deycke, Lominsky, etc.). When low concentrations are used (1 per cent or less) there is no loss of acid-fast characteristics, but there is supposedly a

[1] From the Tice Laboratories, a detail of the Municipal Tuberculosis Sanitarium (Dr. Frederick Tice, President), Chicago, Illinois.

[2] From the University of Illinois Department of Bacteriology and Public Health (Dr. Lloyd Arnold).

[3] From the Illinois State Department of Public Health, Research Division (Dr. Lloyd Arnold).

decrease in virulence of the bacteria (Calmette and Lominsky). On the other hand, cholesterol enhances the virulence. The combination of cholesterol and lecithin acts synergistically and renders the tubercle bacillus more virulent according to Lominsky; yet Calmette employed bile which contains both fats for the attenuation of *BCG*.

Phospholipins differ in their action according to their source (Levene). The object of this experiment was mainly to see the effect of the crude homologous phospholipins extracted from *BCG* on the growth of this organism.

METHOD OF OBTAINING THE CRUDE PHOSPHOLIPIN FRACTION (A MODIFIED BOQUET AND NÈGRE METHOD)

BCG was grown in the usual way as for vaccine on Sauton medium for 21 to 30 days. The growths were pooled, filtered, and washed with saline solution until the fluid returned clear. (The organisms were first autoclaved for 15 to 30 minutes at 120°C.) The bacilli were then dried in the incubator (37.5°C.) or oven (55°C.), and, when dry, ground to a fine powder. The latter was weighed, and to each gram 100 cc. of acetone was added. Extraction at room temperature with frequent shakings was carried out for from 36 to 48 hours. The acetone was filtered off, and the precipitate washed with clean acetone several times. The residue was dried again in the incubator, and again ground to a fine powder. For each gram of pulverized residue, 100 cc. of methyl alcohol was added, and extraction was carried out in the incubator (37.5°C.) for from 12 to 14 days, agitating frequently.

The extract was filtered through a Berkefeld filter, and the fluid portion was distilled under 35 to 40 lbs. pressure at 60°C. To the residue, which was a light tan, thick, paste-like substance, glass beads were added to emulsify this mass. Sauton (pH 7.2) was added slowly until an even emulsion resulted. Finally, more Sauton was added to equalize the amount of methyl alcohol used in the extraction. The emulsion was grayish-white, the color of skimmed milk, and under the microscope there was an even distribution of small globules. Into 250-cc. florence flasks, 150 cc. of this emulsion was poured. The fluid was stoppered and sterilized in 120°C. for one hour. (The emulsion did not change color after this procedure. According to Long this would mean no disintegration of the phospholipins.)

An emulsion of equal intensity was made with egg-lecithin (Merck) 0.4 gm. for each 100 cc. of Sauton.

The bacillus of Calmette and Guérin was grown on both types of media mentioned above, and also on plain Sauton at a pH of 7.2. Cultural characteristics, bacillary morphology, animal inoculations, complement fixations, and tuberculin-testing were carried out.

CULTURAL CHARACTERISTICS

Sauton plus crude phospholipins of BCG: The original culture was taken from a flat veil of the organism grown on Sauton (10 days old) once removed from potato medium. The first subculture presented at the end of 10 days a flat veil covering half the surface of the fluid with small irregular elevated islands. By a tenfold magnification, one noted that the flat part of the veil was granular. With subculturing, the percentage of elevated coiled islands increased. The 7th subculture grew very slowly at first, but after the second week a delicate granular veil appeared, which, upon aging, developed numerous elevated coiled colonies. The 8th generation grew luxuriantly in the form of a veil, while the 9th subculture was retarded in its growth, and here many elevated coiled islands were noted. The 10th transfer usually was much retarded in growth, and quickly sank to the bottom of the flasks.

Frequent subcultures on solid egg media (Loewenstein) of pH 6.5 and 7.8 yielded the usual large granular coiled and the occasional finely granular flat colonies on pH of 6.5; growth was rare on pH of 7.8. On potato medium the typical coiled colonies appeared.

Sauton plus egg-lecithin (Merck); 0.4 gm. for every 100 cc. of solution: The growth upon this medium was not dissimilar to that of the above except that it was much slower. After 5 generations the growth became very sluggish, and only a small area of the fluid became covered by a roughly granular elevated surface growth. The latter quickly sank to the bottom of the flask.

Subcultures on solid egg medium as well as on potato medium resulted in the typical large granular type of colony.

MORPHOLOGICAL CHARACTERISTICS (BACTERIAL)

Bacilli grown on homologous lecithin plus Sauton: There seemed to be differences in the morphology of the bacilli, depending upon age, rapidity and type of growth. The original bacillus was long, slender, granular and acid-fast. In the flask of the third generation (20 to 23 days old) these organisms were plumper and the granulations larger. In the flask of the fifth generation (10 days old) this was still the case with the

elevated coiled colonies (figure 4); but smears of the flat veil-like portion showed numerous small and large granules, the majority being acid-fast. Bacilli, when present, were very small and curved. Smears taken from the eighth generation (20 days old) presented granules of various sizes and shapes, with only a few acid-fast forms. The bacilli of the ninth subculture (5 days old) again presented the long, slender, granular acid-fast forms, not dissimilar to the original culture. In like manner, the bacillary morphology of the cultures on egg-lecithin varied. In interpreting the above, it must be borne in mind that the age of the transplant is not synonymous with the age of the organism, as growth is not always uniform. At times, pleomorphism was noted in the same culture. That a cycle of bacillary growth occurs was strongly suggested.

Animal inoculations: procedure: Guinea pigs were inoculated intracardiacly every four days for 3 doses of 5 mgm. each with *BCG* vaccine (V), grown on Sauton 21 to 30 days; *BCG*, grown on egg-lecithin plus Sauton for one generation (L_1) and three generations (L_3); *BCG*, grown on the crude phospholipins of *BCG* plus Sauton for three generations (L_{Tb3}) and for nine generations (L_{Tb9}). In each case the bacilli were washed with saline solution until the fluid returned clear. Four young animals under one week old were fed vaccine, to which equal parts of 0.4 per cent egg-lecithin were added (the two incubated for 2 hours) for 3 days (total dose, 30 mgm. of vaccine plus 3 cc. of a 0.4 per cent lecithin emulsion). As controls, vaccine plus egg-lecithin treated as above was inoculated into guinea pigs intracardiacly every 4 days for 3 doses (total dose, 15 mgm. *BCG* + 1.5 cc. of a 0.4 per cent lecithin solution); phospholipins of *BCG* were injected intracardiacly for one or two doses, and then continued by the peritoneal route until a total of 4 doses was given (total dose, 30 mgm. of crude phospholipins); phospholipins of *BCG* plus human serum (5 parts serum to 1 part phospholipin) (total dose, 10 mgm. of crude phospholipins).

Complement fixation and skin sensitivity to Old Tuberculin were determined at first weekly, then biweekly, and finally monthly over a period of about one year. Antigen "methylique" (Boquet and Nègre) was used as that for complement fixation.

Table 1 gives the results of this study. It appears that L_{Tb3} gave the quickest serological response, being 80 per cent positive after 5 weeks. It had the highest percentage of reactors after 7 weeks, but after 3 months was preceded by L_{Tb9} and V + Lec. Of the oral group and the group receiving only phospholipins or phospholipins plus serum, no com-

plement-fixing bodies could be detected in the doses given. The amount of antigen necessary to fix a constant amount of complement and serum was not dissimilar in any of the above positive-reacting groups. (Positive reactions were found within dilutions of antigen of 1:100 to 1:500.)

Tuberculin reactions became 100 per cent positive after 3 weeks in the L_3, L_{Tb3}, and V + Lec. groups, and remained so after the 3rd month. L_1 gave only 50 per cent positive reactors. The control and oral groups were all negative.

Subsequent results are not recorded in table form, as some of the animals were killed and others died of intercurrent infection. After 10

TABLE 1

SUBSTANCES INJECTED	NUMBER OF ANIMALS	COMPLEMENT FIXATION			TUBERCULIN REACTION		
		Per cent positive after 5 weeks	Per cent positive after 7 weeks	Per cent positive after 3 months	Per cent positive after 5 weeks	Per cent positive after 7 weeks	Per cent positive after 3 months
V	7	0	66	60	43	100	100
L_1	6	50	50	50	66	50	50
L_3	3	0	66	33	100	100	100
L_{Tb3}	5	80	80	60	100	100	100
L_{Tb9}	5	25	66	100	80	100	100
V + Lec.	3	0	66	100	100	100	100
V + Lec. (oral)	4	0	0	0	0	0	0
Phos.	3	0	0	0	0	0	0
Phos. + serum	3	0	0	0	0	0	0

V = *BCG* vaccine. L_1 = 1st generation on egg-lecithin of *BCG*. L_3 = 3rd generation. L_{Tb3} = 3rd generation on phospholipins of *BCG*. L_{Tb9} = 9th generation. Lec. = egg lecithin. Phos. = phospholipins of *BCG*.

months, however, the surviving animals gave the same tuberculin response as they did at the end of the 3-month period. The complement-fixation tests became negative after 8 months for those surviving in the L_1, L_3, and V + Lec. groups; were still positive after 9 months for the L_{Tb3} group; 50 per cent positive for the L_{Tb9} group after 6 months; and 50 per cent positive for the V group after 11 months.

COMMENT

From a cultural standpoint *BCG*, when grown upon its own crude phospholipin, adapts itself more readily, growing more luxuriantly and for a greater number of generations than when a heterologous lecithin is

Fig. 1

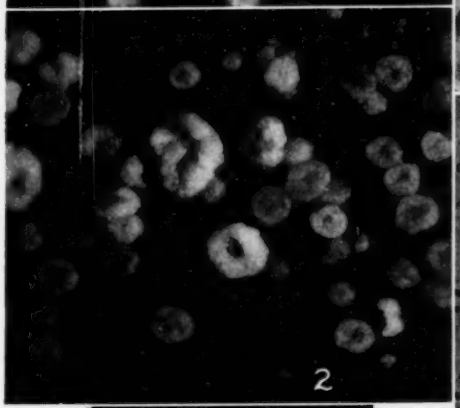

Fig. 2

Fig. 3

Fig. 4

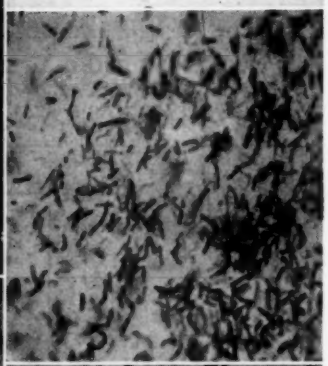

Fig. 5

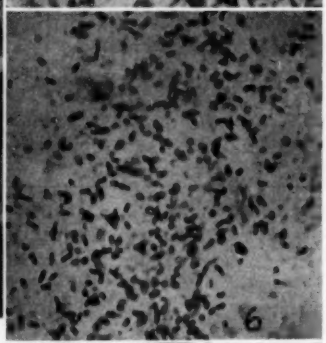

Fig. 6

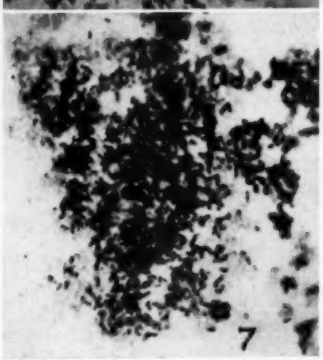

Fig. 7

used. Immunologically, from this study, *BCG* when grown upon the former medium produced antibodies for this lipoid, more rapidly, and in a greater percentage of animals, than the same organism grown on egg-lecithin or without the addition of fat, and over a longer period of time than when a heterologous lecithin was simply added to the organism.

The rôle of simple absorption of phospholipins by the *BCG* must be strongly considered. In many instances, the original culture-medium emulsion, which was very cloudy, became clear after an adequate growth of the organism had occurred. This clearing was not a result of simple settling of the phospholipins. To minimize the source of error resulting from absorption, numerous washings of the bacilli were made. Also,

Fig. 1. Colonies with edges sloping into the media. This strain was grown for 4 generations mixed with cholesterol in oil on Loewenstein's medium (pH 7.2), and followed by 3 generations on the same medium without the use of the fats. Age of colony, 3 months. Note the finely granular surface, and compare with fig. 2.

Fig. 2. Typical crater-like colonies, the same strain as before transferred in the same way at the same time. Note the large granular constituents.

Fig. 3. White smooth colonies, grown in Kolle flasks on Loewenstein's medium (pH 7.2) after mixing with cholesterol in oil (also found with lecithin in oil). Age of colony, one month (4th generation).

Fig. 4. Smear from homologous lecithin plus Sauton culture (5th generation) from an elevated, coiled colony showing plump bacilli with large granulations as well as filamentous forms.

Fig. 5. Smear from surface of bile-potato. Note the long, rather slender bacilli showing some granulation. These were all acid-fast.

Fig. 6. Smear from a flat colony of lecithin in olive oil in Loewenstein's medium (2nd generation). Note the short plump bacilli with numerous granules, many being free and acid-negative.

Fig. 7. Smear taken from flat colonies of fig. 1 in this series, showing granular and bacillary forms. Smear of fig. 2 reveals the usual slender granular bacilli.

phospholipins of *BCG*, alone or attached to another protein (human serum), given in huge doses, failed to produce antibodies by the method described.

The phospholipins did not seem to have affected the reactions to Old Tuberculin (except L_1). A strict relationship between complement-fixing bodies to antigen "methylique" and the tuberculin reaction could not be established.

According to Anderson, and Boquet and Nègre, tubercle bacilli containing more fat (and also phospholipins) are more virulent. Corper, however, reported a lesser amount of fat in an S virulent strain that he isolated than in the R avirulent strain of the same bacillus. This is the

reverse of the findings of Nègre and Boquet. Assuming that there was an increased amount of phospholipins in the above organisms, as noted by complement-fixation tests, the question of an increased virulence of these organisms must be considered. Postmortem examinations of all the animals in this study yielded no evidence of progressive tuberculosis.

B. THE EFFECT OF CHOLESTEROL OR LECITHIN DISSOLVED IN OLIVE OIL ON BCG

As has already been mentioned, Lominsky claims that tubercle bacilli grown on cholesterol produces a more virulent strain of this organism. An attempt was made to culture *BCG* in the presence of cholesterol or lecithin. As these lipoids are soluble in small amounts in neutral oil, the latter method was employed.

CHOLESTEROL IN OIL

Cholesterol (Merck) in 0.2 per cent amounts was dissolved in olive oil by the aid of heating in a water-bath. After cooling, this solution in 2- to 3-cc. amounts was mixed with colonies of *BCG* taken from a 10-day-old Sauton culture. By this method the organisms were easily put in suspension. The mixture was allowed to stand for a few minutes to a half-hour at room temperature or in the incubator, and seeded upon Loewenstein's malachite-green egg medium (pH 6.5, 7.2, 7.8); both tubes and Kolle flasks were used.

Growth progressed to only a moderate degree, and presented the usual large, granular, coiled colonies (figure 2), as well as very small granular flat colonies (figure 1). The flat colonies upon subculture for from 4 to 5 generations yielded a small percentage (10 to 30 per cent) of creamy white, flat, smooth colonies (figure 3). These varied in size from pinhead to 8 mm. in diameter; were transferable for one or two more generations; and then ceased to grow. Subcultures on egg media without fat gave the usual colony morphology.

Animals inoculated with the white colonies described above did not develop progressive tuberculosis, nor was the virulence enhanced.

Staining by the Ziehl-Neelsen method revealed the bacilli to be acid-fast, the white colonies included. These bacilli were shorter and plumper than usual, and were granular.

Egg-lecithin in olive oil; (0.4 gm. of egg-lecithin to 100 cc. of olive oil): The same procedure was followed here as with cholesterol. Except for the fact that growth was even less prolific than above, the results were

not dissimilar. White, flat, smooth and glistening colonies (figure 3) were found at times in the 4th, 5th and 6th generations, but these could not be maintained in subsequent transfers.

The bacillary morphology in this series of transfers was of interest. The original culture was composed of long, slender, filamentous and slightly granular bacilli (figure 5). The 2nd generation on fat media yielded bacilli that were short, plump, with many acid-fast granules (figure 6), whereas the 5th generation again presented slender filamentous forms.

Animals inoculated with the morphologically smooth white colonies showed no evidences of progressive tuberculosis.

COMMENT

The use of cholesterol and lecithin dissolved in oil for the growth of *BCG* produced smooth white colonies in the true sense. They were not dissimilar to the colonies described by Pinner. These organisms were avirulent and could not be sustained after subculture for a long period of time.

When lecithin was employed, variations in the bacillary morphology appeared which suggested a cycle of growth. It will be recalled that Mellon described a definite sexual and asexual cycle when he grew tubercle bacilli on a lecithin-rich medium (brain from which fat was partially extracted). The work of Kahn, Enderlein, Lindegren, etc., also suggests a cycle in the growth of these organisms.

BCG, grown on olive oil added to Sauton, yielded very little growth, of a slimy nature, and entirely dissimilar to the above growths.

GENERAL SUMMARY

The addition of crude *BCG* phospholipins, egg lecithin or cholesterol to media upon which the bacillus of Calmette and Guérin was grown caused changes in the colony morphology of the bacillus, such as finely granular, sloping colonies (figure 1) or actual smooth, white colonies (figure 3). These colonies, however, reverted to their original large granular type after one or more transfers or refused to grow entirely. There was no increase in virulence as noted by animal inoculations.

Of the fats used, growth was most prolific when the homologous crude phospholipin was used, and the latter organisms called forth a prompter and more lasting response in the host of complement-fixing bodies for this lipin. The tuberculin reaction was not noticeably affected.

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CARDIAC FAILURE SECONDARY TO CHRONIC PULMONARY TUBERCULOSIS

A Necroptic and Clinical Study[1]

GEZA NEMET[2] AND MILTON B. ROSENBLATT[3]

Despite the scepticism evinced a relatively short time ago, cardiac failure secondary to diseases of the pulmonary vessels or lungs is now generally accepted as a distinct clinical entity. The studies of Wiggers (1), Moschcowitz (2), and others have demonstrated the mechanism of this type of failure to be one of increasing resistance in the pulmonary circulation, due to narrowing of the arteriolar and capillary beds, with resulting hypertrophy and dilatation of the right side of the heart.

Pulmonary hypertension may be due rarely to a primary obliterating pulmonary arterial disease. Such cases have been described by Ayerza (3), Arrilaga (4), Warthin (5), and Bacon and Apfelbach (6). In several instances the arterial disease was proved to be of syphilitic origin. More commonly, this condition is secondary to diseases of the lungs, bronchi and pleura. The so-called emphysema heart is one of its best-known examples. Regardless of the cause of the increased resistance in the pulmonary circulation, the pathogenesis of enlargement of the right ventricle is the same. Hypertension of the lesser circulation may also be due to mitral disease, but the clinical picture is not exactly analogous in view of the other cardiac changes present in addition to right ventricular enlargement.

Chronic pulmonary tuberculosis may produce changes in the pulmonary circulation in either its destructive phase by caseation and cavitation, or, in its reparative phase, by parenchymal fibrosis or intrapleural adhesions. Collapse-therapy measures, such as artificial pneumothorax, phrenic-nerve interruption, or thoracoplasty also produce circulatory changes. The extensive lung involvement seen in this disease combined with the relatively long duration of illness would seem to make a group of tuberculosis cases ideal for the study of the effects

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of pulmonary disease upon the heart. Stated briefly, the main problems under consideration were (1) the incidence of cardiac enlargement in chronic pulmonary tuberculosis, (2) the characteristics of such enlargement, and (3) the clinical recognition.

The survey comprised all the patients that came to necropsy on the Tuberculosis Division of the Montefiore Hospital for a period of one year. There were 71 patients, of which 21 were discarded because, on gross examination, there was no evidence of any hypertrophy or dilatation of significance of any of the chambers of the heart. In the remaining 50 cases there were 7 instances of left ventricular hypertrophy; 5 associated with right ventricular enlargement and 2 isolated. In all instances the hypertrophy of the left ventricle was slight and one of the 7 cases had a history of previous hypertension. There were no valvular lesions. The right ventricle was found definitely hypertrophied in 33 cases; 24 times alone, 4 times in combination with hypertrophy of the left ventricle, 4 times in combination with hypertrophy of the right auricle, and once in combination with both. In 3 of the 33 enlargements, hypertrophy was demonstrated only on microscopic examination. Accordingly, out of a total of 71 necropsies, the right ventricle was found hypertrophied in 46.5 per cent of the cases, and hypertrophied by itself in 33.8 per cent. These figures tend to correspond with those of Hirsch (7) who found a 35 per cent incidence among 120 cases of pulmonary tuberculosis. There were 16 patients in whom there was found dilatation of the right side of the heart but no right ventricular hypertrophy. Table 1 describes in detail the findings of the Pathology Department in the examination of the 50 enlarged hearts.

Generally speaking, enlargement due to right ventricular hypertrophy was found to be more relative than absolute. The right ventricle often occupied three-fourths or more of the anterior surface of the heart, and yet, with but few exceptions, the total weights of these organs were below normal. There were 24 male cadavers, among which the average weight was 270 gm. and 9 females with average weight of 257 gm. There was but one instance in which the weight exceeded 350 gm. and this was 450 gm. in a male. Hypertrophy of the walls of the right ventricle was not excessive in any instance. The average thickness associated with moderate ventricular enlargement was 5 to 7 mm. and in one case it was 9 mm. Pathological and radiographic observations have repeatedly shown that the heart in the patient with chronic progressive pulmonary tuberculosis is smaller than that found among normal

subjects. In necropsy studies of 100 tuberculosis patients without hypertension or valvular disease, King and Hansen (9) found the average weight among males to be 318.9 gm. and among females 220 gm. Comparing age and sex with normal figures, they found the heart of the tuberculosis patient to weigh distinctly less. The so-called dropped heart is a very common X-ray finding and Schmidt (10), in a roentgenological study of 750 patients with chronic pulmonary tuberculosis of varying degrees of progression, found it in 146 (19.5 per cent) instances. King and Hansen, in studying the cardiothoracic index, found much lower indices among the tuberculosis patients as compared with normal controls. Many explanations have been offered for the small heart in the tuberculous, among which are toxaemia and participation of the myocardium in the generalized muscular atrophy of the body and compensatory emphysema.

In none of the cases with right ventricular hypertrophy were there any important changes in the coronary arteries. Many of the latter were thickened and showed atherosclerotic patches, but all were patent. In one instance there was a healed myocardial infarct in the region of the interventricular septum. There was no significant valvular disease found; 2 cases showed healed rheumatic lesions on the aortic valves. There was one instance of arteriosclerosis of the pulmonary arteries, with thrombosis of the main lower branch.

Parietal pericardial adhesions were found in most of the hearts. Twenty-eight of the 33 hypertrophied right ventricles were associated with adhesions and also 12 of the 16 dilated right ventricles without hypertrophy. The adhesions, however, were not extensive. In 8 instances there were associated pericardial effusions. These effusions were serous, and ranged in amount from 50 to 200 cc. In one instance the pericardium was calcified and in that case, also, there were amyloid changes in the myocardium. Although the incidence of pericarditis was high among the hearts with right ventricular hypertrophy, it was equally high among those with dilatation only. Furthermore, the 21 hearts with neither dilatation nor hypertrophy originally discarded because of no enlargement also showed a similar frequency of pericardial lesions. These observations coupled with the small extent of the pericardial adhesions would tend to eliminate pericarditis as a significant factor in the enlargement of the right ventricles. In a review of the literature, particularly emphasizing Norris's studies, Rigler (8) finds that only 5 per cent of patients with pulmonary tuberculosis have peri-

TABLE 1

Pathological study of enlarged hearts of tuberculosis patients

CASE	WEIGHT IN GRAMS	LEFT AURICLE	LEFT VENTRICLE	RIGHT AURICLE	RIGHT VENTRICLE	PERICARDIUM	VALVES	CORONARY ARTERIES
1	320	Negative	Negative	Negative	Hypertrophied	Adherent	Negative	Slight thickening
2	350	Negative	Hypertrophied	Dilated	Hypertrophied & dilated	Negative	Negative	Negative
3	180	Negative	Negative	Dilated	Dilated	Adherent	Negative	Negative
4	340	Negative	Hypertrophied	Dilated & hypertrophied	Dilated & hypertrophied	Adherent	Negative	Negative
5	280	Negative	Dilated	Negative	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
6	350	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent	Negative	Negative
7	220	Negative	Negative	Dilated	Dilated	Negative	Negative	Negative
8	230	Negative	Negative	Hypertrophied	Dilated & hypertrophied	Adherent	Negative	Negative
9	260	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent	Negative	Negative
10	270	Negative	Dilated & hypertrophied	Dilated	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
11	240	Negative	Negative	Negative	Dilated	Negative	Negative	Negative
12	260	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
13	210	Dilated	Dilated	Dilated	Dilated & hypertrophied	Negative	Negative	Narrow; patent
14	200	Negative	Negative	Negative	Hypertrophied	Negative	Negative	Negative
15	300	Negative	Dilated	Negative	Dilated	Adherent	Negative	Atheroma; patent
16	260	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Negative
17	150	Negative	Negative	Dilated	Dilated	Negative	Negative	Negative
18	220	Negative	Negative	Dilated & hypertrophied	Dilated & hypertrophied	Adherent	Negative	Negative
19	290	Negative	Negative	Dilated	Dilated	Adherent	Calcified mitral ring	Thickened
20	170	Dilated	Negative	Negative	Hypertrophied	Adherent	Negative	Atheroma; patent
21	350	Negative	Hypertrophied	Negative	Dilated	Adherent	Negative	Negative
22	320	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Narrow; patent
23	280	Negative	Negative	Dilated	Dilated	Negative	Negative	Negative
24	450	Negative	Dilated	Dilated & hypertrophied	Dilated & hypertrophied	Adherent; effusion	Calcific mitral & aortic	Atheroma; patent

25	300	Negative	Negative	Dilated & hypertrophied	Dilated & hypertrophied	Adherent	Negative	Negative
26	220	Negative	Negative	Negative	Hypertrophied	Adherent	Negative	Negative
27	230	Negative	Negative	Negative	Dilated	Adherent; effusion	Negative	Negative
28	250	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Negative
29	230	Negative	Negative	Negative	Dilated	Adherent	Negative	Negative
30	350	Dilated & hypertrophied	Hypertrophied	Negative	Dilated & hypertrophied	Negative	Calcific aortic	Calcific; patent
31	330	Negative	Hypertrophied	Dilated & hypertrophied	Dilated & hypertrophied	Adherent	Negative	Thickened; patent
32	350	Negative	Negative	Dilated & hypertrophied	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
33	185	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Negative
34	210	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent; calcific	Negative	Negative
35	320	Negative	Negative	Dilated	Dilated	Adherent; effusion	Negative	Thickened; patent
36	290	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent	Negative	Thickened; patent
37	240	Negative	Negative	Negative	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
38	220	Negative	Negative	Negative	Dilated & hypertrophied	Adherent; effusion	Negative	Negative
39	240	Negative	Negative	Dilated & hypertrophied	Dilated	Adherent	Negative	Negative
40	280	Negative	Dilated	Dilated	Dilated	Adherent	Negative	Negative
41	310	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent	Healed rheumatic aortic	Negative
42	220	Negative	Negative	Negative	Dilated & hypertrophied	Negative	Negative	Negative
43	250	Negative	Negative	Negative	Dilated	Adherent	Negative	Negative
44	180	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Healed rheumatic aortic	Atheroma; patent
45	210	Negative	Negative	Dilated	Dilated	Negative	Negative	Negative
46	350	Dilated	Dilated & hypertrophied	Negative	Dilated	Adherent	Atheroma	Occluded left descending branch
47	230	Negative	Negative	Dilated	Dilated & hypertrophied	Adherent	Atheroma	Atheroma; patent
48	200	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Negative
49	200	Negative	Negative	Negative	Dilated	Adherent	Negative	Negative
50	190	Negative	Negative	Negative	Dilated & hypertrophied	Adherent	Negative	Negative

carditis. This is at variance with our results, which show an incidence of over 56 per cent for the total number of cases. In reviewing Norris's work a possible explanation for this discrepancy is suggested in that the latter excluded cases of minimal involvement.

CLINICAL FEATURES

The group of 33 cases with hypertrophied right ventricles consisted of 24 males and 9 females. The majority of the men were in the fifth, sixth and seventh decades; the majority of the women in the fourth and fifth decades. While it is impossible to determine accurately the duration of the tuberculous disease without radiographic evidence of the onset, an attempt was made to estimate the duration of illness approximately. The figures below are based on the time-interval between onset of first symptoms and admission to the hospital. The range of the clinical duration of illness was wide, varying from one to forty years. However, most of the patients were ill over 3 years and there were but 6 instances of 2 years or less. The duration of illness of these cardiac tuberculous cases was not significant, but was rather similar to what is generally observed among all tuberculosis patients.

We were particularly interested in studying the nature of the tuberculous process in these patients with reference to the occurrence of haematogenous lesions. In this type of tuberculosis the widespread distribution of miliary tubercles favors the production of increased resistance in the pulmonary circulation and hence right ventricular hypertrophy. We are not referring to pulmonary lesions produced by acute miliary tuberculosis or to terminal haematogenous spreads, but to those cases in which the pathogenesis was definitely haematogenous and in which occurred several disseminations with lesions of varying stages and sizes. Associated with these tubercles are marked fibrotic changes in the surrounding lung tissue. These productive tuberculous nodules are located in the walls of lymph- and blood-vessels and in the interlobular and alveolar septa. They show little tendency toward progression, but instead tend toward fibrosis and, in view of the widespread character of the process in both lungs, there results considerable diminution of the capillary bed. For this phase of the work we were very dependent on radiographic studies. We feel, however, that the number of instances which we found does not include many cases which had a haematogenous pathogenesis, but, as the disease progressed, the miliary lesions were replaced by caseation, cavitation, and fibrosis, so that a

diagnosis could not be made. In several instances we were able to secure early roentgen films, and thus establish the haematogenous character of the process. Of the 33 cases of right ventricular hypertrophy 11 (33.3 per cent) showed definite miliary tuberculosis. This is slightly higher than was found by Miller (11) in a study of all types of pulmonary tuberculosis (20 to 30 per cent). It is to be emphasized that, at the time of study, these 11 cases showed active and progressive disease. In general all the 33 cases had extensive bilateral involvement and practically all had large cavities.

The complications associated with the pulmonary lesions in these cases were of no special importance except that those that showed extrathoracic tuberculosis, such as osseous or genitourinary involvement, emphasized the haematogenous mode of spread. Amyloidosis was occasionally significant when renal involvement produced oedema which had to be differentiated from that of cardiac origin. The Wassermann test was negative in all instances.

In the study of the clinical features of these patients it was often found difficult to classify such symptoms as dyspnoea and cyanosis as being due to pulmonary or cardiac insufficiency, or possibly to both. However, when either symptom developed or became more severe in association with such features as hepatomegaly and peripheral oedema, it was reasonable to assume a cardiac relationship. Practically all the patients with right ventricular hypertrophy showed dyspnoea at some time. In a few it was noted terminally only, but in the majority it was present from the time of admission and progressed slowly. Orthopnoea was observed rarely, except as a terminal phenomenon.

Cyanosis was observed in two-thirds of the cases (23) and usually in association with dyspnoea. When observations were possible, it was often noted that dyspnoea and cyanosis began simultaneously. There were seven instances in which dyspnoea was present without cyanosis and three instances in which neither dyspnoea nor cyanosis was present to any remarkable degree. These latter cases showed unusual features, in that one died of uraemia, another of terminal haemoptysis, and the third of oedema of the glottis. It is quite possible that if these complications had not supervened these patients would have followed a clinical course similar to the rest. Cyanosis was of varying degrees, and was most prominent on the cheeks, tip of the nose, lips, elbows, finger tips, knees and toes. Distention of the neck veins was present in one-third of the patients. Venous pressure readings did not parallel the

degree of venous distention. Many instances of considerably dilated veins were associated with normal pressure readings, and, conversely, there were several occasions of venous pressures over 20 cm. of water with very slight distention of the veins.

The liver was enlarged clinically in 14 of the cases (42.4 per cent). In 5 instances the liver first became palpable during hospitalization, and progressive enlargement paralleled the increasing severity of dyspnoea and cyanosis. There were 2 cases in which hepatomegaly was noted terminally only.

Peripheral oedema was present in 15 of the cases (45.4 per cent). It was usually moderate and confined to the ankles and pretibial region. In two instances the oedema was noted on admission and in the rest of the patients it developed under observation gradually becoming more extensive. Ascites and effusions in the pleural cavities were not observed. In one definite instance of right ventricular failure not included in this series moderate ascites was observed.

Erythrocyte counts showed no instances of polycythaemia. The highest blood-count was 5,400,000, which rose to 6,280,000 with respective haemoglobins of 80 and 98 per cent. The remainder of the blood-counts ranged between 3,000,000 and 5,000,000, with ten of the counts between 3 and 4 million and 20 between 4 and 5 million. The corresponding haemoglobin studies showed equal numbers of cases between 50 and 70 per cent and 70 and 90 per cent. There were but 10 patients with red blood cell counts above 4 million and haemoglobin determinations above 80 per cent. These figures did not differ from counts obtained from all types of patients on the Tuberculosis Division.

Studies of the blood-pressure in the right-ventricular hypertrophy cases showed but one instance of hypertension. This patient on necropsy showed hypertrophy of both ventricles. In the remainder of the patients the systolic tension ranged between 90 and 130 mm. and the diastolic between 50 and 90 mm. In most cases there was very little change in the tension until terminally. In a few instances there were noted declines of from 40 to 60 mm. in both systolic and diastolic measurements. It is impossible to state whether these changes were gradual or sudden, as the readings were taken at long intervals.

Despite the fact that cardiac enlargement was present on necropsy in these cases, there was only one instance of the 33 in which it was observed clinically, that is, by X-ray film or fluoroscopy. On the basis of subsequent observations of individual cases, we feel that the ab-

sence of radiographic enlargement can be explained by the fact that such enlargement presents itself late in the course of the disease, and in most instances comparative X-rays were not taken a short time before death. Most of these patients were not suspected of definite cardiac disease, and it was considered unnecessary to take frequent serial X-rays of patients with progressive bilateral disease. However, there were a few instances in which X-rays, taken a very short time before death, showed no enlargement. Fluoroscopy of these patients was also negative, but it must be realized that cardiac fluoroscopy in the presence of extensive pulmonary disease is most unsatisfactory. These latter cases are to be considered among the exceptions. We have subsequently observed that, in most instances, serial X-rays and fluoroscopy will demonstrate cardiac enlargement in the patient with right ventricular failure. This enlargement may occur in a patient in a relatively short time, and often only X-rays, terminally, will demonstrate it. Roentgenological cardiac enlargement may vary from prominence of the pulmonic conus to generalized enlargement of all chambers, with the heart occupying the greater part of the thoracic cage. Early enlargement of the right ventricle produces changes in contour of the left upper and middle portions of the cardiac outline in the form of increased prominence of the pulmonic conus and artery. With additional enlargement, the right ventricle extends more and more upward and to the left, producing a straightening of the left cardiac border and even actual bulging of the conus. As the right ventricle increases still further in size, it displaces the left ventricle posteriorly, and finally occupies the greater portion of the left border. This change of contour may take place without any apparent increase in the transverse diameter of the heart. Expansion of the lower part of the right ventricle (inflow tract) is recognized in the left anterior oblique position as increased bulging of the right lower contour. Increased width of the diaphragmatic contour of the heart in this position also indicates right ventricular enlargement. This is due to displacement of the right auricle outward and upward. It is to be emphasized, however, that enlargement of the cardiac shadow to the left and upward is indicative of right ventricular extension even in the absence of enlargement of the right cardiac border.

Owing to the physical condition of the patients very few electrocardiographic studies were made. In the six electrocardiograms that were taken there were seen no major disturbances in rhythm; one showed premature auricular beats, one showed premature ventricular beats,

and one showed A-V conduction disturbance. Physical examination of all the 33 cases disclosed at no time any cardiac arrhythmia. It is interesting to note that Parkinson and Clark-Kennedy (12) found that one-fifth of patients dying in congestive failure with normal rhythm were subjects of chronic pulmonary disease, and that Smith (13) observed that in patients who died in congestive failure secondary to chronic pulmonary disease the heart failed in normal rhythm. Although only one of our cases showed right-axis deviation, there were three that showed negative T waves in the third lead, and two of these also showed negative T waves in the second lead. Many extensive electrocardiographic studies have been made on patients with chronic pulmonary tuberculosis. Some of the results are analyzed below.

Boas and Mann (14), in a study of 97 patients with chronic pulmonary tuberculosis, found 28 instances of right-axis deviation and 29 of left-axis deviation. The former group was comprised mostly of younger patients and the latter of older patients. They concluded that right-axis deviation was found just as frequently in patients with ulcerative pulmonary tuberculosis as with chronic fibroid phthisis. Simon and Baum (15), in a study of 250 cases, found a 10 per cent incidence of both left- and right-axis deviation. They found several instances of inverted T waves, and concluded that inverted T waves in the second and third leads were of serious prognostic import in patients with caseous cavernous tuberculosis. Heaton (16), in a series of 304 cases, found a 7.9 per cent incidence of right-axis deviation and a 16.1 per cent incidence of left-axis deviation. He also emphasized the bad prognostic importance of inverted T waves in more than one lead. Master (17), although he did not study cases of pulmonary tuberculosis, made an important contribution to the subject of right ventricular enlargement. He found that right-axis deviation with inversion of the T wave in the third lead alone, or in leads two and three, was characteristic of right ventricular enlargement, and that negative T waves in the second, or second and third leads, were commonly associated with right ventricular preponderance. His studies also showed that, when enlargement of the right ventricle was very marked, there was inversion of the T in both leads, and, when enlargement was less extensive, there was inversion only in the third lead. When right-axis deviation occurred without any T-wave changes, right ventricular enlargement was very slight.

Correlation between clinical and pathological findings was not gen-

erally present in our cases. Actually, only 11 of the 33 cases (33.3 per cent) were recognized clinically as having heart disease. The diagnosis was made in several instances only a short time before death, when the cardiac symptoms became prominent. In the remaining 22 cases the diagnosis was entirely postmortem. The cause of death in these latter cases was either progression of the pulmonary disease, or related causes, such as terminal haemoptysis, inanition, or spontaneous pneumothorax. There were 2 cases that died in uraemia, secondary to pyonephrosis and amyloidosis, respectively. With present diagnostic standards, there is really but one positive criterion for right ventricular failure and that is roentgen evidence of cardiac enlargement. In the absence of this sign, the diagnosis must be made on an association of clinical features which includes dyspnoea, cyanosis, venous distention, hepatomegaly, peripheral oedema, and absence of hypertension. Of secondary importance are electrocardiographic alterations, increased venous pressure, polycythaemia, and accentuation of the pulmonic second sound. The patient with chronic pulmonary tuberculosis will often show dyspnoea and cyanosis in the absence of cardiac changes as a result of anoxaemia due to destruction of pulmonary tissue. Also, palpable livers are a common finding among tuberculosis patients, due either to atrophy of the abdominal muscles, or to actual enlargement as a result of fatty or amyloid changes. Oedema may be due to causes other than cardiac. The diagnosis of right ventricular failure must therefore be made more on the sequence of the onset of the various clinical features than on any individual symptoms or signs. Blood-chemistry studies of the serum proteins are often necessary to exclude a renal or nutritional origin of the oedema. In actual practice, however, it is not difficult to differentiate the individual case of right heart failure. The real problem lies in being unable to differentiate all the cases. As was shown above, only one-third of the 33 cases were diagnosed premortem. While it is true that *cardiac enlargement* and *cardiac failure* are by no means synonymous terms, nevertheless the former represents an earlier phase of the latter condition. It seems rational, therefore, that, just as there is a transition period of pathological changes, there should be a transition period before the patient goes into recognizable cardiac failure in which the cardiac symptoms are obscured by those of the pulmonary disease. At present it is impossible to distinguish clinically between pulmonary and cardiac insufficiency in the early stages of cardiac failure. Possibly chemical studies of the oxygen and carbon-

dioxide saturation of arterial and venous blood will prove of assistance in this direction.

Two of the 11 cases recognized clinically were diagnosed on admission, and the remaining nine developed cardiac failure under observation. The onset was sudden, and usually with moderately severe symptoms, but in a few days the findings were quite marked and the duration of life after cardiac failure had set in was relatively brief. Two patients lived 1 week; 2 lived 2 weeks; 2 lived 3 weeks; 1 lived 4 weeks; 1 lived 8 weeks; and 1 lived 12 weeks. The two patients who were admitted to the hospital in cardiac failure lived 2 and 6 weeks, respectively. The abrupt character of the onset of right ventricular failure has been noted by other observers and has been attributed to tricuspid incompetence or acute anoxaemia. It seems to us that Starling's "Law of the Heart" (18), with respect to the stretching of cardiac muscle fibres, might be applicable to this phenomenon.

While the cause of death in these cases was cardiac failure, at the same time we should not overlook the importance of the underlying pulmonary lesion. As a matter of fact, in two instances terminal exacerbations of the pulmonary tuberculosis paralleled the occurrence of cardiac failure. Inasmuch as all the patients had extensive bilateral disease, the figures given above may not correctly represent the effect of right ventricular failure on the duration of life. We have observed on several occasions that patients with minimal pulmonary tuberculosis in whom the cardiac changes were due more to chronic bronchitis and bronchiectasis had a much greater duration of life than those with active tuberculosis. We have also noted that, despite the degree of failure, these patients showed a good response to therapy. The two case-histories below of patients not included in the series describe the differences in the clinical course of right ventricular failure as it occurs in the patient with active pulmonary tuberculosis and with healed pulmonary tuberculosis.

Case 1: S. K., a 39-year-old male, was admitted with an extensive bilateral pulmonary tuberculosis of two years' duration. There were large cavities in both upper lobes. The course of illness in the hospital was active and progressive. Six months after admission the patient suddenly became markedly dyspnoeic and cyanotic, and within 24 hours showed hepatomegaly and peripheral oedema. There was marked venous distention and the venous pressure was 19 cm. The patient became increasingly comatose, and died within 48 hours of the onset of the cardiac symptoms. Figures 1 and 2 illus-

trate the progression of the pulmonary disease and the cardiac enlargement. On necropsy, the right ventricle was found dilated and hypertrophied and the right auricle dilated. The left auricle and ventricle were negative, and the valves and coronary arteries were also negative.

Case 2: H. L., a 63-year-old male, was admitted with a history of productive cough of 35 years' duration. Examination showed an old fibrotic phthisis limited to the apical regions associated with extensive emphysema, bronchitis and bronchiectasis. The course in the hospital was uneventful for almost two years. During this period, the patient was ambulant and afebrile, and showed no signs of active disease. Sputum was persistently negative. The only clinical features of importance were dyspnoea and cyanosis, which were

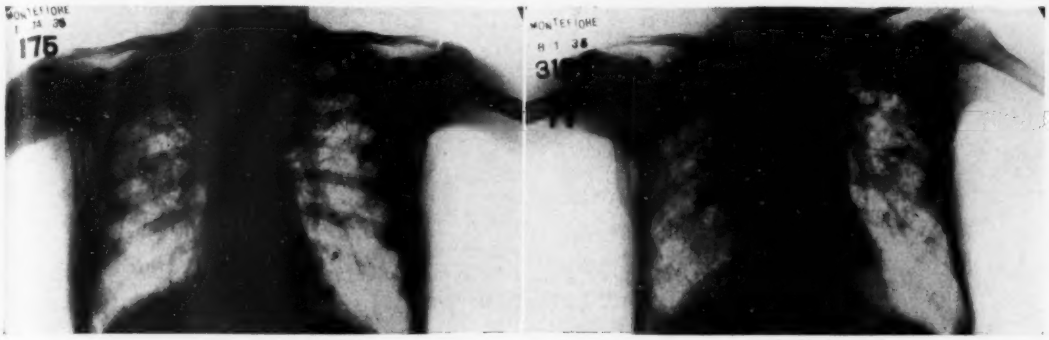

Fig. 1 Fig. 2

CASE 1

X-ray series showing course of right ventricular failure

Fig. 1. January 14, 1935. Fibrocaseous cavitary involvement of both upper lobes. The heart is small but there is prominence of the pulmonic conus.

Fig. 2. August 1, 1935. Pulmonary infiltration much more extensive. Pulmonic conus shows definite bulging, and there is an increase in the transverse diameter of the heart.

but moderately severe, and the patient was retained in the institution solely as a custodial case. Two years after admission, dyspnoea and cyanosis abruptly became very marked, the liver became enlarged and within 24 hours there was oedema of both lower extremities. Figures 3, 4, and 5 demonstrate the inactive character of the pulmonary process over a period of years, and the progression of the cardiac enlargement. On intensive diuretic therapy, all the cardiac symptoms and signs improved, and, two weeks after the onset of cardiac failure, X-ray showed a marked diminution in the size of the heart shadow. Improvement continued for about a month, with progressive diminution in the size of the right ventricle (figure 6). The patient then became very uncoöperative with respect to following instructions about bed-rest, restricted fluid and salt intake, etc., and the only effective therapy after a

while was periodic injections of mercurial diuretics. The heart gradually increased in size, and 6 months later became just as large as it had been at the onset of failure (figure 7). It is to be emphasized that, during this entire period of cardiac insufficiency, the patient was semiambulant. Eleven months after failure began, the patient suddenly became very weak and cyanotic and died the following day. On necropsy, the anterior surface of the heart was composed entirely of the right ventricle which was markedly hypertrophied and dilated. The left ventricle was normal as were also the valves and coronary arteries.

Case 2 lived for 11 months in a degree of cardiac failure far greater than case 1 which lived but two days. Inasmuch as the major difference between the two cases was that one had healed minimal tuberculosis and the other had extensive bilateral active disease, it is reasonable to assume a relationship between the character of the pulmonary lesion and the effect of cardiac failure on the duration of life. Investigation of our series of cases along these lines revealed that the two patients who lived 8 and 12 weeks, respectively, had dominantly fibrotic lesions; and that the latter patient, even though in cardiac failure, actually died of a terminal haemoptysis due to his tuberculosis. After observing a fairly large number of cases of pulmonary tuberculosis with right heart failure during the past five years, we are led to believe that in the tuberculosis patient who dies in cardiac failure the more important cause of death is the pulmonary disease. One might say more properly that the patient died with cardiac failure than because of it.

In practically all of the cases diagnosed clinically (10 out of 11) there was found on necropsy dilatation of the right ventricle in addition to

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Fig. 3. August 21, 1930. Fibrotic infiltrations, both upper lobes. No significant cardiac enlargement.

Fig. 4. March 7, 1932. Pulmonary lesion unchanged. Slight prominence of the pulmonic conus and moderate central congestion.

Fig. 5. September 22, 1932. Definite bulging of pulmonic conus and of right lower contour of heart. Transverse diameter of heart considerably increased. The left ventricle shows no apparent enlargement. The pulmonary lesion remains unchanged.

Fig. 6. December 13, 1932. There is marked diminution in the size of the heart. Both the left upper and right lower borders are distinctly less prominent. The transverse diameter is also reduced. Pulmonary disease unchanged.

Fig. 7. June 16, 1933. The heart is enlarged again as in figure 5. Both the outflow and inflow tracts of the right ventricle are once more increased in size. The left ventricle is unaffected as before. No changes in the tuberculosis.

Fig. 8. June 16, 1933. Same as figure 7, but in the left anterior oblique position. There is bulging of the right lower contour and increased width of the heart. Note the large retrocardiac space indicating absence of enlargement of the left ventricle.

Fig. 3

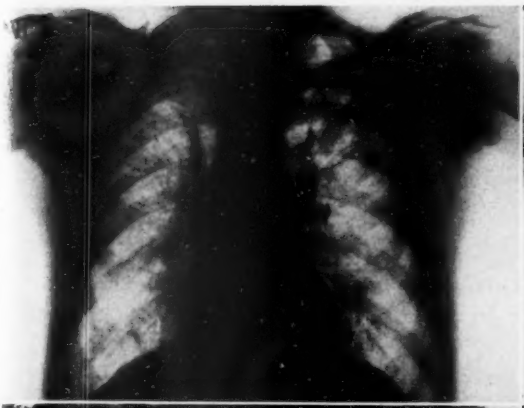

Fig. 4

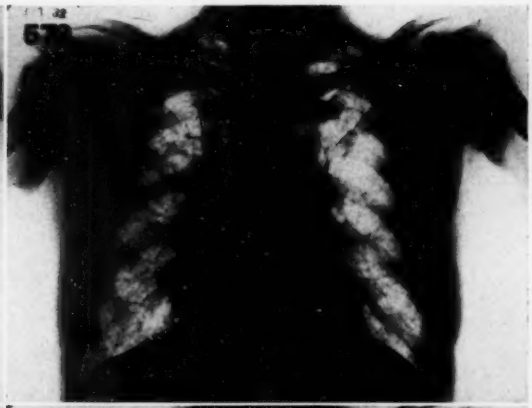

Fig. 5

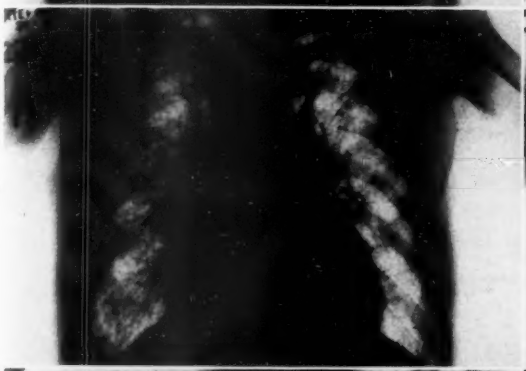

Fig. 6

Fig. 7

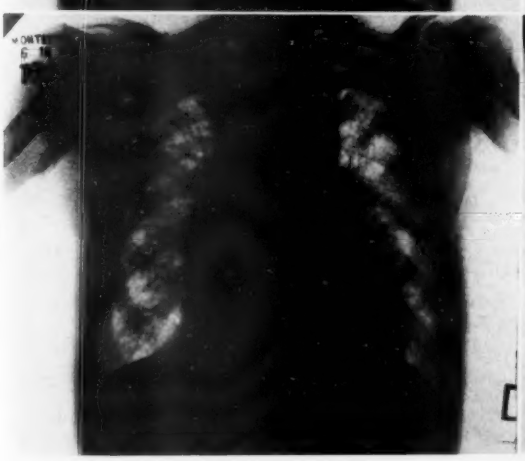

Fig. 8

CASE 2

X-ray series showing course of right ventricular failure

hypertrophy. The dilatation was especially noted in the outflow tract. In the 22 cases with hypertrophied right ventricles but no clinical signs of cardiac failure, dilatation was found 16 times.

There was a group of 16 patients in the original series in whom dilatation of the right ventricle was present on necropsy without any hypertrophic changes. Four of these patients died in cardiac failure. It is of considerable interest that one of them was in cardiac failure for a period of over 10 weeks. The duration of life in the other three after cardiac failure had occurred was, respectively, 2 days, 1 week and 4 weeks, just as in the group with hypertrophy the duration of life in cardiac failure varied inversely with the degree of pulmonary activity. The remaining 12 patients with dilated right ventricles died of the following causes: progression of the pulmonary disease, 5; inanition, 2; spontaneous pneumothorax, 2; uraemia, 1; diabetic acidosis, 1; and pulmonary embolus, 1.

SUMMARY

1. A study of the 71 patients who came to necropsy on the Tuberculosis Division of the Montefiore Hospital during a period of one year revealed 33 instances (46.5 per cent) of right ventricular hypertrophy.

2. None of the 33 cases were associated with any significant coronary-artery disease, valvular disease or hypertension. There was one instance of antecedent hypertension in a patient with hypertrophy of both ventricles.

3. Despite enlargement of the right ventricle, the hearts, in general, were smaller than normal.

4. The duration of the pulmonary disease in these patients did not differ from that seen in all types of tuberculosis patients. All the cases had extensive bilateral involvement and one-third showed definite haematogenous lesions.

5. Recapitulation of the most significant symptoms revealed the occurrence of dyspnoea 30 times (90.9 per cent); of cyanosis 23 times (69.6 per cent); of hepatomegaly 14 times (42.4 per cent); and of peripheral oedema 15 times (45.4 per cent). Inconsistencies between the degree of venous distention and venous pressure were noted.

6. There were too few electrocardiographic studies from which to draw any conclusions. However, review of the literature reveals that right-axis deviation with inversion of the T wave in the second and third leads may be considered indicative of right ventricular enlargement.

7. Eleven of the 33 cases (33.3 per cent) were recognized during life

as having heart disease; in the remaining 22 (66.7 per cent) the diagnosis was entirely postmortem.

8. It is felt that the inability to distinguish clinically between pulmonary insufficiency and cardiac insufficiency was largely responsible for the low percentage of diagnoses. Dyspnoea, cyanosis, venous distention, hepatomegaly, and even oedema may be attributable to causes other than cardiac failure in the patient with chronic pulmonary tuberculosis.

9. The duration of life after cardiac failure had occurred was relatively brief, and depended considerably upon the character of the underlying pulmonary process.

10. The cardinal sign of right ventricular failure is enlargement on fluoroscopy or X-ray film. Demonstration of this sign will be facilitated, especially in the early stages, by detailed and frequent studies.

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THE CARDIOGENIC THEORY OF PULMONARY EMPHYSEMA[1]

A New Theory

EPHRAIM KOROL[2]

CLASSIFICATION OF EMPHYSEMA

From a clinical viewpoint, all cases of emphysema may be classified as (1) compensatory, (2) obstructive, or (3) nonobstructive emphysema.

The compensatory form develops in cases in which large portions of the lung have been rendered functionless from whatever cause, and is brought about by the overactivity of the functioning portions of the lungs.

Obstructive emphysema is encountered in cases of narrowing of the air passages, whether caused by spasm or by obstructive lesions in the upper or lower respiratory channels. In this class belong the emphysema associated with asthma and the cases of bullous emphysema. This form always causes marked symptoms and physical signs, and is the form which was first described in the medical literature (Laennec (1)).

We shall concern ourselves with the less spectacular but the much commoner, nonobstructive, type of emphysema. It develops silently, beginning in early childhood (Virchow (2), Louis (3)), it progresses with the age of the individual, so that by middle life it is found postmortem in practically all cases (Waters (4), Duschnitz (5)). In its earlier stages it is confined to the anterior margins of the upper lobes, the left lung being involved more than the right (Louis (3), Jenner (6), Kaufmann (7), Flint (8), Johnson (9), Duschnitz (5), Hektoen and Riesman (10), Beattie and Dickson (11), and many others). The earlier and more extensive involvement of the left upper lobe is a characteristic and invariable postmortem finding in emphysema. We believe, however, that the aetiological significance of this preference for the left upper lobe has not been duly appreciated.

[1] Published with the permission of the Medical Director of the Veterans Administration, who is not responsible for opinions expressed or conclusions drawn by the author.

[2] Veterans Administration, Lincoln, Nebraska.

REVIEW OF THE THEORIES OF EMPHYSEMA

The following theories have been offered to explain the localization of emphysema in the anterior lung borders.

1. The Expiratory Theory. This is the oldest theory. It was advanced early in the history of the disease, first in Germany (Mendelssohn (12), Fuchs (13)) and later in England (Jenner (6)). It was based on the observation that the pulmonary apex, a common seat of emphysema, is overinflated during expiratory efforts made with closed glottis. It was also known that, in defects of the chest wall, lung hernias appear during straining (expiratory) efforts. It was commonly believed that occupations requiring sustained expiratory efforts, such as glass-blowing, predispose to pulmonary emphysema. The paradoxical inflation of the apex and of lung hernias during expiration was correctly attributed to the lack of bony support and the deficiency in musculature in these regions. It was concluded that the vulnerability of the anterior pulmonary margins is due to the same factors, that is, these regions also have insufficient bone and muscle support and during expiratory efforts they suffer paradoxical inflation. Jenner (6) explained the greater prevalence of emphysema in the left lung by the stomach being more yielding to expiratory efforts than is the solid liver.

Objections to the Expiratory Theory. Pulmonary regions which breathe paradoxically are actuated by the same muscular forces as the normally breathing lobules, and there is no reason why they should become overinflated. Paradoxical breathing normally occurs in the interspaces of the lateral chest wall (Hitzenberg 14) as seen in the Litten phenomenon, yet the underlying lung is not a common site of emphysema. The cases of advanced apical emphysema that have been examined postmortem (Fischer (15), Dorendorf (16), Zinn and Siebert (17), Hayaschi (18)) have shown the emphysematous blebs to depend on strictures along the passages, generally caused by tuberculous scars. In other words, the apical emphysema is really a form of obstructive emphysema. The apices are vulnerable because of their disposition to tuberculous infection. It is not true that the anterior pulmonary margins breathe paradoxically under normal conditions. Physical and X-ray examinations show that these areas invariably inflate in inspiration and deflate in expiration. Only in cases of extensive disease of the chest wall, such as fracture of the sternum, or of the lungs, such as lobular pneumonia or obstructive emphysema, will the lung undergo

paradoxical movement. If paradoxical breathing occurs in cases of emphysema, it is a manifestation of the disease and not a cause of it.

In this connection it should be pointed out that observations on large series of glass-blowers (Prettin and Liebkind (19)) and of wind-instrument players (Fischer (20)) have not shown these occupations to predispose to emphysema. Animal experimentation has also shown that prolonged expiratory obstruction does not produce emphysema (Nissen (21), Loeb (22)).

Jenner's ideas regarding the transmission of the respiratory pressure fluctuations through the stomach and liver are contrary to Pascal's law governing the transmission of pressures through fluids. The stomach on the left side should counteract any tendency to paradoxical breathing on this side.

2. The Thoracogenic Theories of Emphysema. According to these theories the changes in the chest wall which occur in the declining years of life bring about an enlargement of the chest with secondary emphysema of the lungs.

Freund's theory (23). The degenerative changes in the costal cartilages which begin in the fourth decade of life are associated with swelling and enlargement of the cartilages. The changes commence in the first cartilage on the right side and later involve the other ribs. The enlarged cartilage pushes the rib away from the sternum on each side, bringing about a gradual enlargement of the chest. The lungs enlarge concurrently. The cartilages finally calcify and lose their flexibility, the thorax becoming rigid and uniformly dilated. Freund claimed (24) that the beginning of emphysematous changes in the anterior lung borders lend support to his theory.

Objections to Freund's theory. Experimental enlargement of the thoracic cage in animals (Nissen (21)) has not resulted in pulmonary emphysema but in readjustment of the viscera and elevation of the diaphragm. It is hard to understand why gradual enlargement of the chest should produce enlargement of the lungs only in the vicinity of the heart; also, how changes beginning in the cartilages of the right side of the chest can account for emphysema which first begins in the left lung. Freund has not shown that the costal cartilages actually increase in length. Sumita (25) restudied the degenerative changes in the costal cartilages in general and confirmed the anatomical findings made by Freund. However, he found no enlargement of the chest in

cases of rigid thorax, except when emphysema was present. In other words, it is the emphysema and not the changes in the cartilages which causes enlargement of the chest. In a similar study, Schenker (26) found that, of thirty-one cases with degeneration of all the cartilages, only twelve had barrel-shaped chests. Many cases of barrel-chest occur without marked emphysema and cases of advanced emphysema are encountered without chest deformity (Loeschcke (27), Tendeloo (28), Zesas (29), and others). In several of the cases operated on for the relief of emphysema, the resected cartilages presented no changes (Rath (30), Zesas (29), Cohn (31)).

The spinal-curvature theory of pulmonary emphysema. The senescent changes in the spinal column alter the shape of the chest and secondarily cause emphysematous changes in the lungs (Loeschcke (47), Kountz and Alexander (32)). The intervertebral discs undergo thinning and absorption; the body weight causes a collapse of the spine with the formation of a curvature, generally in the upper dorsal region. The anteroposterior diameter of the chest is increased and there results hyperinflation of the anterior pulmonary margins.

The objections in this theory are much the same as those to Freund's theory. The pulmonary changes are found at a much earlier age than that at which spinal deformities set in. Cases of pronounced emphysema occur without spinal changes (Weltz (33)) and many kyphotics are observed without marked emphysema (Van Skramlik (34), Tendeloo (28), and others).

3. The Inspiratory Theory of Emphysema. Pulmonary emphysema depends on the same factors which normally maintain the residual air, namely the expiratory contraction of the bronchi and the tone of the inspiratory muscles. Conditions associated with spasms of the bronchi, such as asthma, and physical efforts and dyspnoeic states and other conditions associated with increased tone of the inspiratory muscles, bring about increased residual air and an elevation of the mean respiratory position. Any demand for increased ventilation of the lung is accompanied by heightened inspiratory tone. The inspiratory muscles being regulated by a nerve centre (Howell (54)) are more efficient than the expiratory muscles, and there results an accumulation of residual air in forced breathing. The deformities of the chest wall and of the spine are secondary to the permanent inflation of the lungs and the tonic contraction of the respiratory muscles occurring in emphysema.

The inspiratory theory is sponsored by Spengler (35), Weltz (33), Tendeloo (28), Van Skramlik (34), Rohrer (36), and others, and is currently the most accepted theory of emphysema. However, like the once popular nutritional theory of emphysema, it does not attempt to explain the peculiar localization of the emphysema in the anterior pulmonary margins.

Plainly, other, as yet unmentioned, factors must be invoked to account for this vulnerability of the anterior pulmonary margins.

THE CARDIOGENIC THEORY OF EMPHYSEMA

Each cardiac contraction, due to the diminution in the size of the heart, exerts a suction effect on the neighboring pulmonary lobules causing an inspiratory movement; the succeeding dilatation of the heart during diastole compresses the contiguous lobules. This respiratory activity of the heart has been long known to physiologists and clinicians, but it has been ignored by the pathologists who have done the bulk of the work on emphysema. Ernst (37), in 1856, observed that in the experimental animal the lung dilates with each systole and retracts in diastole. This observation was repeated by Bamberger (38). Voit (39) measured these respiratory pressure fluctuations with a manometer. Kymographic tracings of the cardiorespiratory movements have been prepared by several authors (Tigerstedt (40), Haycraft and Edie (41)). Voit (39) was the first to describe the cardiorespiratory murmur; this is an inspiratory sound caused by the systolic inrush of air into the lobules neighboring the left ventricle (Lewis (42), Hewlet (43), and many others). This murmur is produced by large and by nervously hyperactive hearts.

The normal adult heart at rest discharges 50 or 60 cc. of blood during each systole (Tigerstedt (40)) and, of course, diminishes in size by this amount. In enlarged hearts, and particularly in mitral and aortic regurgitation, the stroke volume of the heart is much greater; the cardiac contractions are also increased, both in volume and in rate, during physical exercise and during nervous excitement. Although not all the blood discharged from the heart leaves the chest, still in the immediate vicinity of the heart a space of some 50 or 60 cm. is created during each ventricular systole, which space is immediately occupied by inflated lung. The tidal air of the lungs, caused by the respiratory chest movements, averages 500 cc. Bearing in mind that the tidal air is distributed over both lungs while the cardiac impulse is applied to the

neighboring lobules only, it may be seen that the paracardiac lobules are ventilated by the heart action quite as much as by the chest wall. Needless to point out that these paracardiac areas of the lung continue in motion even during physiological apnoea when the bulk of the lung is at rest.

Fluoroscopic observation of opaque bodies in the lungs, such as calcified nodules and drops of lipiodol, shows that these particles are drawn toward the heart with each systole. These movements are strongest near the left ventricle and diminish rapidly as the distance from the heart increases. With large and nervous hearts these movements may exceed the displacement which these particles undergo during the respiratory movements of the chest wall. The volume fluctuations of the heart, and the cardiorespiratory movements depending on them, are greatest in aortic and mitral regurgitation (Williams (44)), also in diseases of the heart associated with hypertension and with hyperthyroidism (Levene and Reid (45)).

Each systole occurring during the inspiratory cycle causes overinflation of the normal lung tissue in the vicinity of the heart; each diastole occurring during expiration causes a forcible compression of these lobules. During expiration the systoles tend to suck stale air from the bronchi into the paracardiac lobules; during inspiration the diastolic dilatation of the heart propels stale air from these lobules into the more peripheral pulmonary areas which are now undergoing inspiratory dilatation. This paradoxical breathing explains the lack of coal pigment in the paracardiac lung tissue: the air circulating in this tissue is largely shut off from the atmosphere and is free of coal dust.

CONCLUSIONS

The anterior pulmonary margins become overinflated by the combined respiratory action of the heart and of the chest wall. The lingular process of the left lung is more emphysematous than the right middle lobe because the left border of the heart has greater respiratory activity than the right border.

THE RELATION BETWEEN PULMONARY EMPHYSEMA AND CARDIOVASCULAR DISEASES

The emphysematous lung is characteristically poor in blood vessels, these gradually undergoing narrowing and obliteration. The right heart meets with increasing resistance in the lungs and undergoes hyper-

trophy and dilatation. It is easy to explain this enlargement of the right heart which is a constant feature in advanced emphysema. However, the left heart is also commonly enlarged in cases of emphysema. This was recorded by Louis (3), early in the history of the disease and has been emphasized by many observers, (Hutchinson (46), Johnson (9), Waters (48), LaFosse (49), Giessen (50), Despreaux (51), Curschmann (52), and others). Some of the observers considered the cardiac enlargement as the primary condition, others came to opposite conclusions. Waters (48) never saw a case of extensive emphysema in which the left as well as the right side of the heart was not affected; he frequently found valvular disease associated with emphysema. Waters thought that the left side of the heart is embarrassed by the displacement of the heart and torsion of the blood vessels caused by the enlarged lungs.

Johnson (9) states that the association of mitral and aortic disease with emphysema is so frequent that it cannot be explained as a mere casual coincidence.

Hutchinson (46) expresses himself as follows: "The impaired circulation through the lungs causes dilatation of the right ventricle which in turn, through the venous and arterial circulation, leads to dilatation of the left ventricle with incompetence of the mitral valve." Despreaux (51) and the adherents of the nutritional theory of emphysema hold that heart disease is primary and emphysema develops as a result of labored breathing and associated bronchitis. Sir Thomas Lewis (42) states that heart failure in emphysema is not a simple affair of pulmonary arterial pressure, and he points out the frequent coëxistence of disease of the left side of the heart. In this connection Lewis ponders over the unexplained frequent enlargement of the right heart in aortic disease and concludes that there must be a hidden source of increased work to which the right heart is subjected in disease of the left side of the heart.

The cardiogenic theory of emphysema explains the association of this condition with all valvular and vascular diseases which are accompanied by hypertrophy of the left ventricle. The decisive factor is the increased stroke-volume of the enlarged heart. In my experience most cases of arterial hypertension, of mitral disease and aortic valvular disease, reaching middle age, show X-ray evidence of extensive emphysema. The enlargement of the right ventricle in aortic disease finds its source in the invariably associated emphysema.

THE PROGRESSION OF THE EMPHYSEMATOUS CHANGES

After the air vesicles bordering the heart have become permanently dilated there is a tendency for the pulmonary changes to spread peripherally. As shown by Ribbert (53), in the emphysematous lobules the bronchioles as well as the blood vessels become elongated and their lumina are narrowed; eventually they lose their capacity to keep open during expiration and begin to act in a check-valve manner, admitting air into the lung in inspiration and entrapping it during expiration.

SUMMARY

1. Emphysema in its earlier stages is confined to the anterior pulmonary margins and is more developed in the lingula of the left lung.

2. The several current theories of emphysema fail to explain this localization of early emphysema in the paracardiac pulmonary lobules.

3. The normal contractions of the heart actuate the contiguous pulmonary lobules, the systolic contraction causing an inspiration, the diastolic dilatation causing an expiratory movement. With large hearts and during physical exercise, this cardiorespiratory activity of the anterior pulmonary margins may equal or exceed the activity caused by the respiratory movements of the chest wall.

The anterior pulmonary margins, particularly that of the left lung, being the most exercised regions of the lungs, become the favorable seat of pulmonary emphysema.

4. Valvular diseases of the heart and functional diseases associated with enlargement and increased cardiac output increase the tendency to emphysema and are quite generally associated with advanced emphysema. The enlargement of the right side of the heart found in cases of hypertension and in aortic disease is to be attributed to the associated pulmonary emphysema.

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COMPARATIVE VENTRICULAR WHITE BLOOD COUNTS IN NORMAL GUINEA PIGS[1]

MORRIS DWORSKI

In spite of many investigations the source of the monocytes that constitute the fundamental response of the tissues to the tubercle bacillus is open to question. Sabin and her coworkers (1) believe that the majority of these cells are produced locally in an infected organ by a proliferation of primitive reticulum cells, but they admit that some of the monocytes may be brought to the focus from other organs by the blood-stream. Gardner (2) suggested that the latter mechanism might be studied by comparing the relative number of monocytes in the blood of the right and left sides of the heart when the lung is the site of a localized tuberculous infection. He reported his preliminary attempts, but his results were inconclusive and demonstrated the need for further observation.

Gardner's technique was an adaptation of that used by Simpson (3) to study the distribution of "circulating macrophages in the blood." The blood samples were withdrawn from the ventricles of the heart while the animal was under ether anaesthesia. Simpson performed repeated punctures upon the same animals and, in so doing, obtained showers of macrophages which others have subsequently come to believe were derived from the traumatized pericardium. Gardner attempted to avoid this dilemma by making his preliminary observations on a series of different animals whose pericardial cavities were dissected away after exposing the heart while the animal was under deep anaesthesia.

The study to be reported represents a continuation of the preliminary work by Gardner. Repeated samples of blood have been withdrawn from two sides of the heart of the same animal without anaesthesia. Criteria for the recognition and elimination of contaminating pericardial cells have been established. The data obtained will be reported in two

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

papers, the first dealing with the blood of normal guinea pigs and the second with that of tuberculous animals.

The first paper consists of a statistical analysis of 300 blood counts from the right and left ventricles of the hearts of 34 normal guinea pigs.

MATERIAL AND METHODS

At the onset, only animals which appeared free from disease were selected and, if any individual showed marked fluctuations of its blood count or appeared ill during the period of observation, it was eliminated. Animals of both sexes were used. Twenty-eight of them were between three and four months old, and the remaining six were between six and twelve months. It is important that animals of the same approximate age be utilized, for it is known that the total white count increases with age (4) (5).

In preliminary trials, blood was obtained from animals anaesthetized with ether, but wide variations occurred in samples from the right and left ventricles which could often be correlated with the depth of the anaesthesia. When blood was secured without ether, no marked fluctuations occurred, and in some animals repeated ventricular counts were approximately the same. The use of an anaesthetic was therefore abandoned.

Standardized Trenner pipettes were used for the total white-cell counts, and the blood diluted 1:20 with 1 per cent acetic acid. Duplicate counts were made and averaged. Differential white counts were made on 200 cells stained supravitally with neutral-red. Sabin's technique (6) for counting human cells was modified, because the guinea-pig blood cell is more permeable to the dye than the human blood cell; and therefore a weaker solution of the neutral-red must be used. By adding 50 drops of a saturated solution of neutral-red (0.25 per cent) to 10 cc. of absolute alcohol, a proper dilution is obtained. These films of the dye are made on slides cleaned according to Dr. Sabin's directions. Though the description of the vitally-stained cells given by Sabin is limited to human blood, the various guinea-pig cells react to the dye in a similar manner and no difficulty is encountered in differentiating them.

To obtain samples of blood the guinea pig is fastened tightly on an animal board. The area over and around the heart is shaved, and painted with iodine. The left ventricle covers a large portion of the ventral surface of the heart. The right ventricle lies to the extreme right edge, and partially underneath the left ventricle. A 24-gauge needle,

1½ inches long, attached to a 1-cc. Luer "tuberculin" syringe is used. The left ventricular blood is secured by inserting the needle at the point of maximum cardiac impulse. There is a definite sensation as the needle penetrates the heart muscle. The venous blood is obtained by inserting the needle perpendicularly about one-half inch to the left of the sternum, and then pushing it obliquely toward the heart. With experience, the two ventricles can be reached with these different approaches. The criterion for the source of the blood is always its color. There is sufficient contrast between the venous and aerated blood to make the identification certain. About 0.3 cc. of blood is aspirated and placed on a paraffine-lined watch-glass. A portion is immediately withdrawn for the total white count. The blood for the supravital smear is then drawn into a paraffined-lined capillary pipette, and a small drop expelled on a cover-slip, which is placed face down on the blank slide stained with neutral-red. The slip is ringed with salvoline to prevent drying, and is incubated at 37°C.

It should be noted that there is often the danger of contaminating the ventricular blood with cells of the pericardial fluid. This pollution occurs rarely in the early punctures. However, in an occasional animal which has been repeatedly bled at frequent intervals, a pericardial effusion develops which must be recognized and discounted in evaluating counts.

Histological section of the hearts of animals repeatedly punctured in this manner reveals the absence of reaction indicative of infection, but there are foci of induration in the pericardium incident to the trauma. This is accompanied by proliferation of the lining mesothelial cells.

The presence of large amounts of pericardial fluid mixed with blood can be detected grossly by a decrease in the viscosity of the blood, as it is drawn into the dilution pipette and by a watery appearance as it spreads on the cover-slip. However, smaller amounts of fluid produce no gross changes in the blood, but in this case the presence of pericardial cells in the smear is indicative of contamination. Blood containing such cells is discarded. A repetition of the puncture within a few minutes will usually yield a pure sample for the pericardium is drained by the first aspiration. Even in the presence of a pericardial effusion, contamination can usually be avoided if the suction is delayed until it is certain that the needle has entered the ventricle.

The cytological characteristics of the types of cells found in normal pericardial fluid have been studied in supravital preparations stained

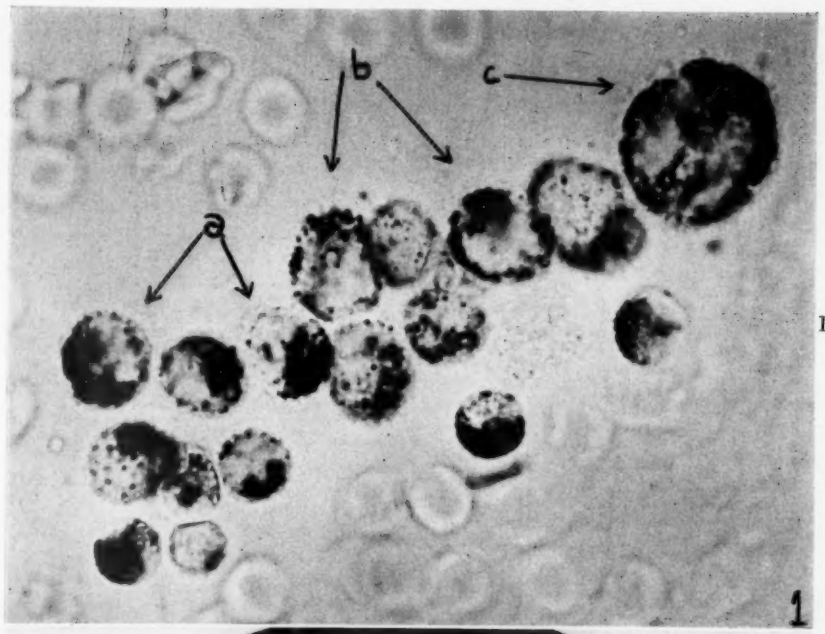


FIG. 1

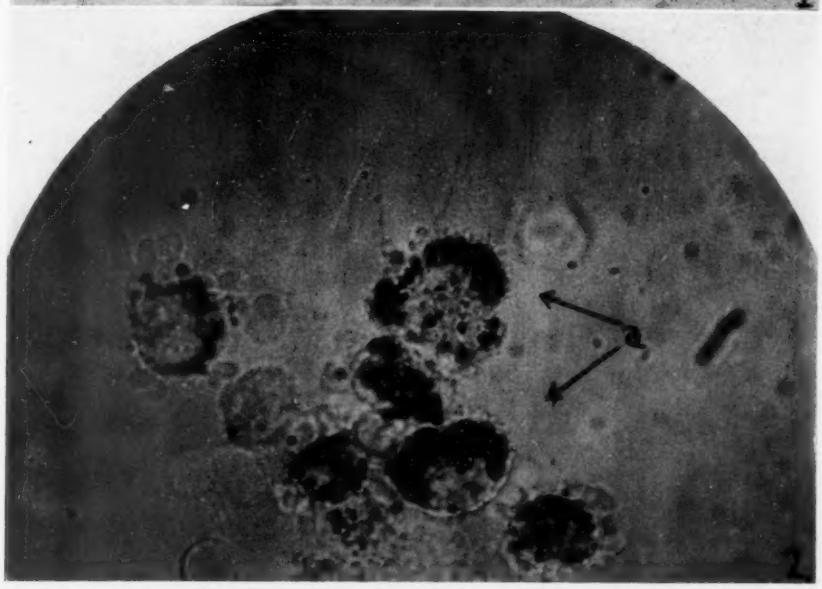
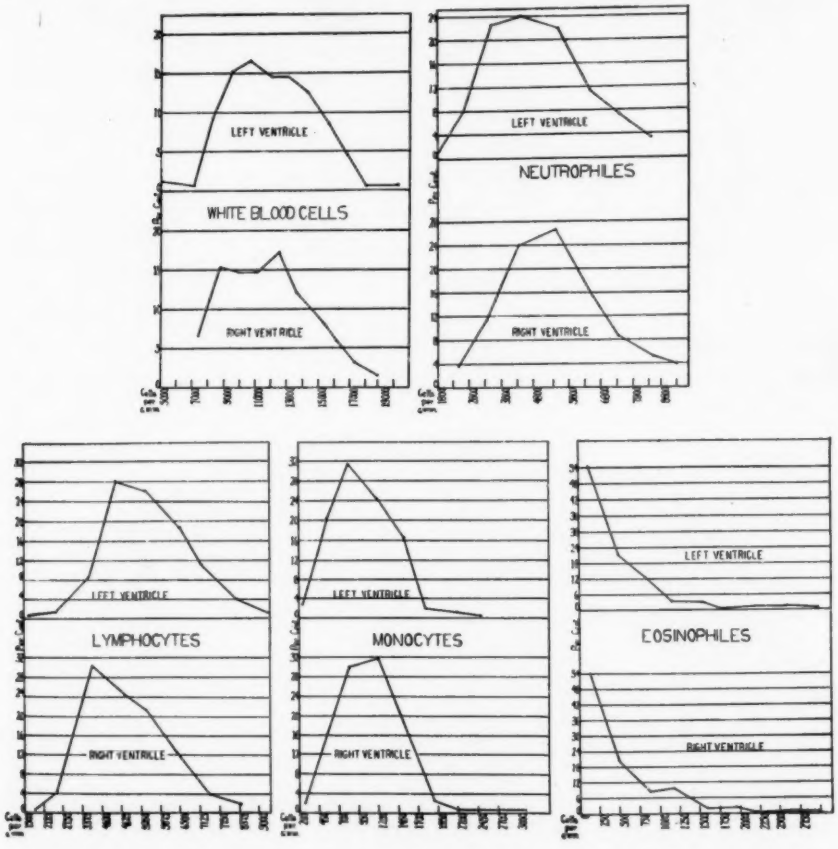


FIG. 2

FIG. 1. Pericardial fluid from a normal guinea pig, × 1150. Stained supravitally with neutral-red. A group of monocytes and a single free macrophage or clasmatocyte are presented: *a* indicates cells with peripherally placed nuclei; *b* with central nuclei; and the cell indicated by *c* is a free macrophage.

FIG. 2. Pericardial fluid from a guinea pig with pericardial effusion produced by repeated ventricle punctures. × 1150. Stained supravitally with neutral-red. This fluid contained 22 per cent of the cells indicated by arrow.

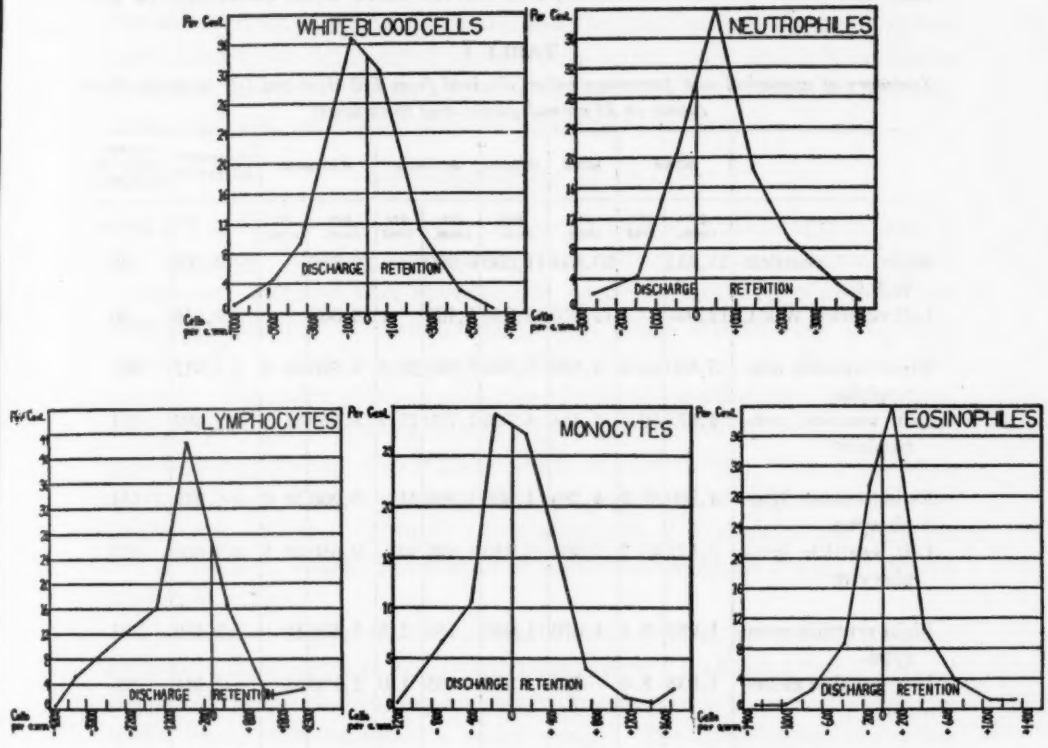
with neutral-red in 40 normal guinea pigs. The fluid for this purpose was obtained by exposing the heart and aspirating directly from the pericardial cavity with a capillary pipette. It was found that the fluid contains an average of 9,091 cells per cmm., and that in the differential count there were about 95 per cent mononuclear cells whose



GRAPH 1. Distribution frequency of numbers of white blood cells, neutrophiles, lymphocytes, monocytes, and eosinophiles per cmm. in per cent.

morphology is similar to the mononuclear phagocytes of the peritoneal fluid (7). The majority of these cells varied from 8 to 20 micra in diameter. In some of them the nucleus is round and centrally placed; in others it is oval or reniform, and peripherally situated. The vitally stained elements may be irregularly distributed without pattern, perinuclear, or in clusters forming a partial rosette. These vacuoles vary in size, stain unevenly, and possess different refractive properties (figure

1, *a* and *b*). In some fluids there were a few large cells (30 to 40 micra in diameter) with abundant cytoplasm, filled with different-sized vacuoles and granules which stained with varying intensity and color. These cells correspond to Sabin, Doan and Cunningham's (8) clasmatocyte, or the free macrophage or histiocyte of other investigators (figure



GRAPH 2. Distribution frequency of numerical differences of white blood cells, neutrophiles, lymphocytes, monocytes, and eosinophiles of right ventricle from left ventricle per cmm. in per cent.

1, *c*). In the stimulated fluid there is an increase of these large cells or macrophages (figure 2, *a*). The fluid cell can be differentiated from the typical blood monocyte, which in typical adult form exhibits a rosette of nonrefractile orange-red vacuoles located in the "Hof" of the nucleus.

GRAPHS

The results of the blood counts have been tabulated as absolute number of cells per cmm. of blood. The distribution curves given in graph

1 were obtained by plotting the actual group means, using group intervals of 1,250 for the total white blood cells, 1,000 for the neutrophiles and lymphocytes, and 350 for the monocytes and eosinophiles. The basophiles were not considered. No attempt has been made to smooth the initial or final values, and actual values have been used throughout this analysis. In all instances, the curves have been extended to the

TABLE 1

Summary of numerical and percentage values obtained from 150 right and left ventricle blood counts on 34 normal guinea pigs (both sexes)

	MEAN		MODE	MEDIAN	MINIMUM		MAXIMUM		STANDARD DEVIATION	COEFFICIENT OF VARIATION
	per cmm.	*per cent*	*per cmm.*	*per cmm.*	*per cmm.*	*per cent*	*per cmm.*	*per cent*		*per cent*
Right ventricle W.B.C.	11,933		10,934	11,600	6,900		19,350		±10,705	89
Left ventricle W.B.C.	12,067		12,016	12,050	5,100		20,000		±9,636	80
Right ventricle neutrophiles	5,540	46.4	4,820	5,300	2,000	20.5	9,550	64.0	±5,917	107
Left ventricle neutrophiles	4,873	40.4	4,354	4,700	1,790	25.5	8,600	61	±7,402	151
Right ventricle lymphocytes	4,760	39.9	4,280	4,600	1,860	24	8,900	59.0	±6,877	144
Left ventricle lymphocytes	5,523	45.7	5,004	5,350	1,680	30	9,650	60.5	±5,668	102
Right ventricle monocytes	1,085	9.1	1,070	1,080	185	2.5	3,100	18	±2,450	225
Left ventricle monocytes	1,038	8.6	735	995	105	1.0	2,100	15	±2,341	225
Right ventricle eosinophiles	537	4.5	−144	310	0	0	3,000	33.0	±2,568	480
Left ventricle eosinophiles	518	4.3	−241	265	0	0	2,970	30.5	±2,551	493

upper limits. The mode was calculated from the empirical formula of Pearson, Mode = Mean — 3 (mean-median).

Distribution curves, representing the numerical differences between the numbers of cells in the right and left ventricles (*R-L*), are given in graph 2. The data for these curves were obtained by grouping the differences, starting with the greatest negative difference. The points represent the mean value of the following group intervals; 2,000 for the

deviations of the total right white blood count from the left, 1,000 for the neutrophiles and lymphocytes, and 300 for the monocytes and eosinophiles.

RESULTS

The results of the blood cell determinations are presented in condensed form in table 1. Distribution frequencies and algebraic deviations have been determined for the cells in the right and left ventricles (graphs 1 and 2). The standard deviations and the coefficients of variations were also calculated and are included in table 1.

INTERPRETATION OF GRAPHS

Right and left ventricle counts: By employing animals of approximately the same age, housing and feeding them alike, a certain degree of uniformity of material was maintained. Any variation in counts is presumably inherent in the animal itself. The distribution frequency curves offer a graphical representation of the range of the individual counts. The total white counts give the lowest coefficients of variation, with 89 per cent for the right, and 80 per cent for the left ventricle. The eosinophiles occupy the highest level of variability with coefficients of variation of 480 per cent and 493 per cent for the right and left ventricles respectively. Though the coefficients of variations are high for the group as a whole, the counts of individual animals fluctuate within a narrow range.

The form of the curves for the white blood cells, neutrophiles, lymphocytes and monocytes of both ventricles (graph 1), shows a fair degree of regularity in the descending and ascending portions, though that for the white blood cells occupies a wider range. The distribution curve for the eosinophiles differs from those for the other cells. The shape of this curve is due to the fact that in some blood samples eosinophiles were not found, and the majority of the counts were small.

In table 2 the mean values of the absolute numbers of cells obtained in this study have been compared with the peripheral blood counts reported by Camp, Luton, Tompkins and Cunningham (9). These investigators made 199 counts on 36 normal guinea pigs, aged 4 to 9 months, using the supravital technique for the differential counts. The comparison discloses that their mean values for the total white blood cells, neutrophiles, lymphocytes, monocytes, and eosinophiles in the peripheral blood are of the same general order as the mean values

obtained in this study for the same cells in the right ventricle. There is also a close agreement between the peripheral total white cells, monocytes, and eosinophiles and the corresponding cells in the left ventricle. But in the case of neutrophiles and lymphocytes there is a marked variation in the relative numbers observed from the peripheral circulation and from the left ventricle. These differences may presumably

TABLE 2

Comparison of blood cell values—ventricular and peripheral means of absolute numbers per cmm.

	300 COUNTS 34 ANIMALS		199 COUNTS 36 ANIMALS (CAMP, *et al.* (9))
	Right ventricle	Left ventricle	Peripheral (ear)
	per cmm.	*per cmm.*	*per cmm.*
White blood cells	11,933	12,067	12,194
Neutrophiles	5,540	4,873	5,761
Lymphocytes	4,760	5,523	4,459
Monocytes	1,085	1,038	1,113
Eosinophiles	537	518	591

TABLE 3

Summary of average differences between right and left ventricle blood cells, obtained from 300 ventricular counts in 34 guinea pigs

	RIGHT = LEFT		RIGHT > LEFT PLUS DEVIATIONS. RETENTION		SUM OF PLUS DEVIATIONS	RIGHT < LEFT NEGATIVE DEVIATIONS. DISCHARGE		SUM OF NEGATIVE DEVIATIONS	RATIO RETENTION / DISCHARGE
	Number of counts	Per cent	Number of counts	Per cent	Retention	Number of counts	Per cent	Overflow	
Total W.B.C.	3	2.0	60	40	+113,400	87	58	−127,025	0.90
Neutrophiles	0	0	109	72.6	+125,295	41	27.3	−32,465	3.86
Lymphocytes	3	2.0	31	20.6	+26,755	116	77.3	−143,425	0.19
Monocytes	1	0.6	78	52	+26,700	71	47.3	−21,870	1.22
Eosinophiles	12	8.0	75	50	+21,750	63	42	−17,635	1.23

be explained as a result of changes taking place within the pulmonary circulation.

Numerical differences of the cells in the right and left ventricle: The algebraic differences of the various classes of cells in the right and left ventricle were determined, the positive values representing retention in the lung and the negative ones a discharge number. In table 3 these differences are summarized and a ratio of retention to discharge is

derived by dividing the sum of the positive values by the negative total. In graph 2, the distribution frequencies of the differences are charted. The resulting graphs approximate probability curves. In the interpretation of these curves, the total area on either side of the ordinate at zero is significant. If the area under the curve to the left of this ordinate is greater than the area to its right, the graph indicates that for this group of animals more cells are leaving than entering the pulmonary circulation; in other words, there is a discharge of cells into the blood-stream previously retained or proliferating in the lung. If, on the other hand, the area is greater to the right of the zero ordinate, a retention of cells has occurred in the lung. The ratios in table 3 express this relation between the two areas of each curve.

DISCUSSION

As it was stated earlier in this paper, the use of an anaesthetic was avoided in obtaining the blood samples. The work of Petersen and Levinson (10) has shown that general anaesthesia increases the permeability of the capillaries and creates a condition of stasis and hyperaemia in the capillary bed of the lung. Such a mechanism would obviously favor periods of retention of blood cells in the lung, followed by their subsequent discharge at undefined intervals. Experience has shown that without anaesthesia the flow of blood through the lungs is only affected by changes in the blood capillaries. In the normal animal there has only been slight variations in repeated counts, taken at intervals of 5 to 60 minutes. Therefore it has been assumed that the short interval elapsing between the collection of the sample from the right and left heart respectively is of no great importance.

A most striking and surprising finding is the consistent discharge of lymphocytes in the blood leaving the lung. In 30 out of 34 animals observed, more of these cells are seen in the effluent blood, an average increase of 863 cells per cmm. per animal. The constancy of this discharge would seem to indicate a generation of new cells from lymphoid areas rather than a change in distribution of cells already in circulation. In one animal 12 counts were made over a period of 67 days and a discharge of lymphocytes was recorded in each count. Although 20 per cent of the counts did indicate retention, the evidence as a whole suggests that these cells may arise in the lymphoid tissue of the lung under normal conditions. Kiyono (11) states that cells originate in those organs whose venous blood contains the largest number of the

particular cell. While histological evidence of germinal centres is lacking in the lymphoid tissues of the lungs in the guinea pig, the areas exhibit numerous cells in mitosis. Under any form of irritation the peripheral lymphoid tissues undergo hyperplasia and become sufficiently large to be visible to the naked eye. The excess of lymphoid cells in the effluent blood of this animal might well be a manifestation of such proliferation within the lung.

In contrast to the discharge of lymphocytes, there is retention of the neutrophile in the lung in 72.6 per cent of the counts, there being an average retention of 667 cells per cmm. per animal. In fact the curve for the lymphocytes (graph 2) is the mirror image of that for the neutrophiles. Since relatively few neutrophiles are seen in the lung tissue of normal animals, this cell may be destroyed in the lung and eliminated through the lymphatics. Such a possibility has been suggested by Aschoff (12) who stated that as the spleen destroys red cells so the lungs may possibly be a "graveyard" for certain groups of white cells.

The data regarding the monocyte are difficult to evaluate, and the evidence submitted does not offer a true indication of the point of origin of this cell. For the group as a whole there is an average retention of 47 monocytes per cmm., but there are variations among different animals and in the same guinea pigs there are fluctuations from day to day. Presumably monocytes are constantly being formed from the reticulum cells in different organs of the body. Under the influence of various stimuli too slight to be considered pathological, the lung at times might produce an excess of such cells which would shortly appear in the effluent blood-stream. Only by studying the effect of a sufficiently potent stimulus applied locally to the lung can such an hypothesis be tested. The data on tuberculous infection to be reported subsequently will be of significance in this connection.

There is a slight retention of eosinophiles equal to 18 cells per cmm. per animal. The individual counts show marked fluctuations.

All cells thus far described were easily identified in the supravital smears. Very rarely a large granular cell was discovered which has not been included in the tabulation. It was considered to be an atypical basophile. Its large granules were oval in shape, refractive and failed to take the stain. Nonmotile neutrophiles were noted infrequently and were present in both ventricles. No abnormal cells such as the clasmatocyte or macrophage were seen except for those originating in the pericardial fluid.

Lymphocytes containing Kurloff bodies were present in varying numbers in all the animals examined. Bender and DeWitt (13) believe that there is a close association between the Kurloff bodies and eosinophilia. To learn whether such a relationship existed, the Kurloff bodies were noted in 36 counts made on 10 guinea pigs aged three to four months. The number of eosinophiles per cmm. were compared with the number of Kurloff bodies per 100 lymphocytes. In this group of animals, no correlation appeared between the number of Kurloff bodies and the eosinophiles.

SUMMARY

Right and left ventricular heart's blood counts have been made upon a group of 34 normal guinea pigs. Differential cell counts are based on smears stained supravitally with neutral-red.

The total number of white blood cells per cmm. of blood is approximately the same in both ventricles and is comparable to figures obtained by others for the peripheral blood.

The polynuclear neutrophiles are higher in the blood of the right heart than in that of the left ventricle, namely, in 73 per cent of the counts. This suggests that at least a portion of these cells may be removed from the circulation and possibly destroyed in the normal lung.

Lymphocytes are in excess in the blood of the left ventricle in 77 per cent of the counts, indicating that cells of this type may enter the lesser circulation within the lung. The guinea pig may be an unusual animal in this respect for its lung, even when apparently normal, contains masses of lymphoid tissue which often exhibit many cells in the process of division.

Monocytes are distributed in approximately the same numbers in the blood before and after it passes through the lungs. There are small variations in favor of one ventricle or the other, which occur from time to time in the same animal and in different animals. A slight excess of monocytes in the left ventricular blood is obviously attributable to errors in observation but, where the difference is marked, it may be due either to local production of these cells in the pulmonary reticulum or to a discharge after a period of accumulation.

Eosinophiles are extremely variable; if there is any trend it is toward retention of these cells within the lung. This is a reasonable supposition since histological examination of the lungs of normal guinea pigs frequently discloses large numbers of these cells within the connective

tissues of the bronchi. No correlation between an eosinophilia and the presence of Kurloff bodies in the lymphocytes could be established.

Pericardial fluid sometimes contaminated the blood samples particularly where repeated punctures were made on the same animal. Such contamination can be avoided by a preliminary puncture to drain the pericardial sac before drawing blood for a count. The pericardial cells when stained supravitally possess the same general characteristics as those from other serous cavities. If they are recognized and excluded no "showers of macrophages" will be found in the blood obtained from the heart.

This problem was suggested by Dr. L. U. Gardner to whom I am grateful for guidance during this study. Also I wish to acknowledge the valuable technical assistance of Mr. Anthony B. Delahant.

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COMPARATIVE VENTRICULAR WHITE BLOOD COUNTS IN EXPERIMENTAL PRIMARY TUBERCULOSIS IN GUINEA PIGS[1]

MORRIS DWORSKI AND ANTHONY B. DELAHANT

To shed light upon the rôle of the blood monocyte as a progenitor of the epithelioid cell in pulmonary tuberculosis, a series of simultaneous counts on the blood cells from the right and left sides of the heart of individual guinea pigs was made. These counts were taken over an extended period previous to and during the phase of tubercle formation in the lung. As already mentioned in a previous communication (1), a technique was developed whereby it was possible to obtain samples of venous and arterial heart's blood with a considerable degree of accuracy and with a minimum amount of injury to the animal. To avoid possible changes induced by anaesthesia, the punctures were made without this procedure.

The previous communication dealt with the quantitative and qualitative differences in the leucocytes of the right and left heart's blood in *normal* guinea pigs. It was shown that the blood, in passing through the lungs, lost many neutrophiles and comparatively few eosinophiles but gained a sufficient number of lymphocytes to justify the assumption that cells of this type proliferate in the pulmonary lymphoid tissue and wander into the blood-stream.

The number of monocytes from the two sides of the heart varied but they did not show any consistent trend. This variation in the counts in apparently normal animals was assumed to be the result of intermittent retention of blood-borne monocytes and of local proliferation within the lung in response to mild irritation by accidentally inhaled foreign bodies. The validity of this assumption is substantiated by the observations on tuberculous animals to be presented in this paper. It appears that, under stimulation of local infection in the lung, monocytes emigrate from the arterial blood into the pulmonary tissues, but they also develop locally from primitive reticulum cells in the lung and

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

then migrate back into the circulation so that at times an excess may appear in the effluent blood.

MATERIAL AND EXPERIMENTAL METHODS

The animals selected for infection had, in most instances, four control blood counts at varying intervals previous to infection. Twenty guinea pigs were studied; sixteen were infected and four were uninfected controls.

The animals, infected in various ways, are divided into four groups: (1) intratracheal injection of an attenuated human type bacillus; (2) inhalation of virulent human bacilli; (3) inhalation infection with attenuated human organisms; (4) uninfected controls.

Group 1 consists of five animals injected intratracheally with 0.5 cc. of a heavy suspension of an attenuated strain of human tubercle bacilli, H_{60}, containing approximately 350 bacilli per oil immersion field after a standard loopful had been spread upon a surface of 1 sq. cm.

Intratracheal inoculation with the above mentioned dosage produces a widespread diffuse tuberculous reaction that subsequently heals by resolution. Its course is illustrated by five animals killed at intervals from 12 to 406 days after infection. Reaction began as a diffuse inflammation; tubercles were present in 26 days, but were healed by the 147th day. In all three animals killed thereafter the only evidence of tuberculosis occurred in the tracheobronchial nodes.

Group 2 was composed of eight animals infected by the inhalation method with a highly virulent human tubercle bacillus, strain H_{68}, (Saranac Laboratory). With a suspension showing an average of two bacilli per oil immersion field they received ten puffs from the vaporizer. The blood of only four of these animals was counted, the remainder were killed at intervals to mark the progress of the disease. A generalized tuberculosis was produced and all the animals had been killed or had died from tuberculosis within 69 days.

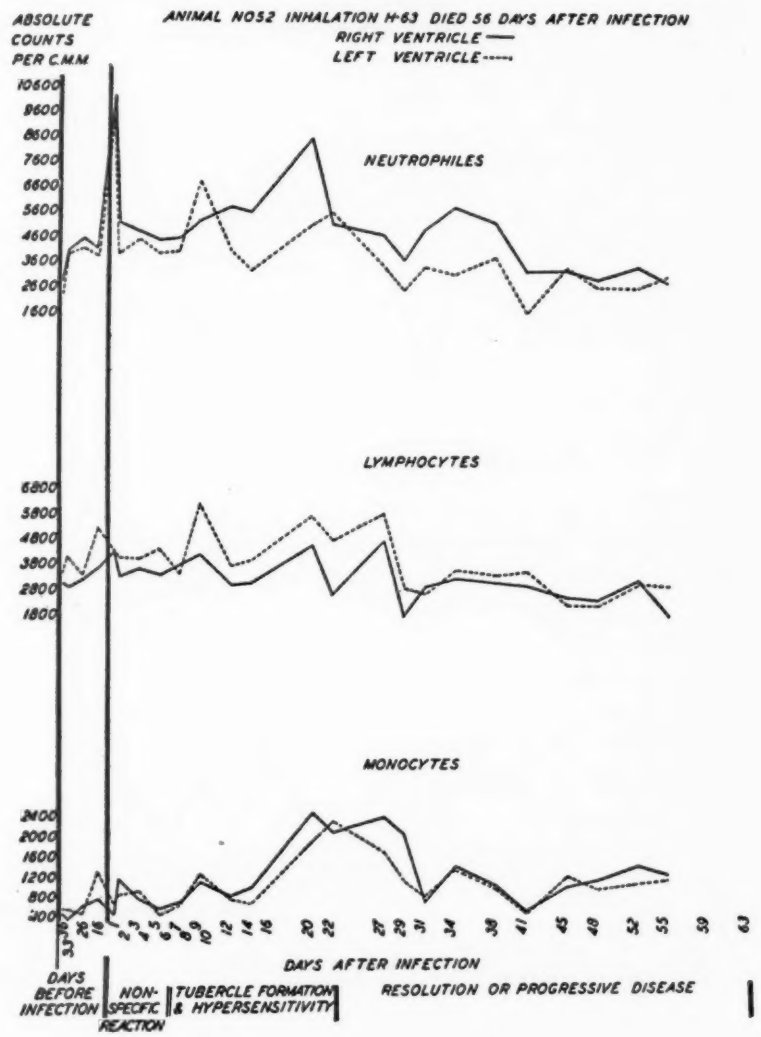
Group 3: Three animals were infected by inhalation of the attenuated human strain R1. They received six puffs from the vaporizor of a suspension exhibiting 15 isolated bacilli per oil immersion field.

Group 4 of uninfected controls numbered four animals.

By the technique described in the former paper (1) simultaneous samples of right and left heart's blood were obtained in different animals at 1, 5, 8 and 24 hours after infection. During the subsequent three weeks, in most instances counts were made every other day. Thereafter two

samples were drawn every week until the 70th day. Standardized Trenner pipettes were used for the white cell counts. Duplicate determinations were made and averaged. Differential white counts were made on 200 cells stained supravitally with neutral-red.

CHART I

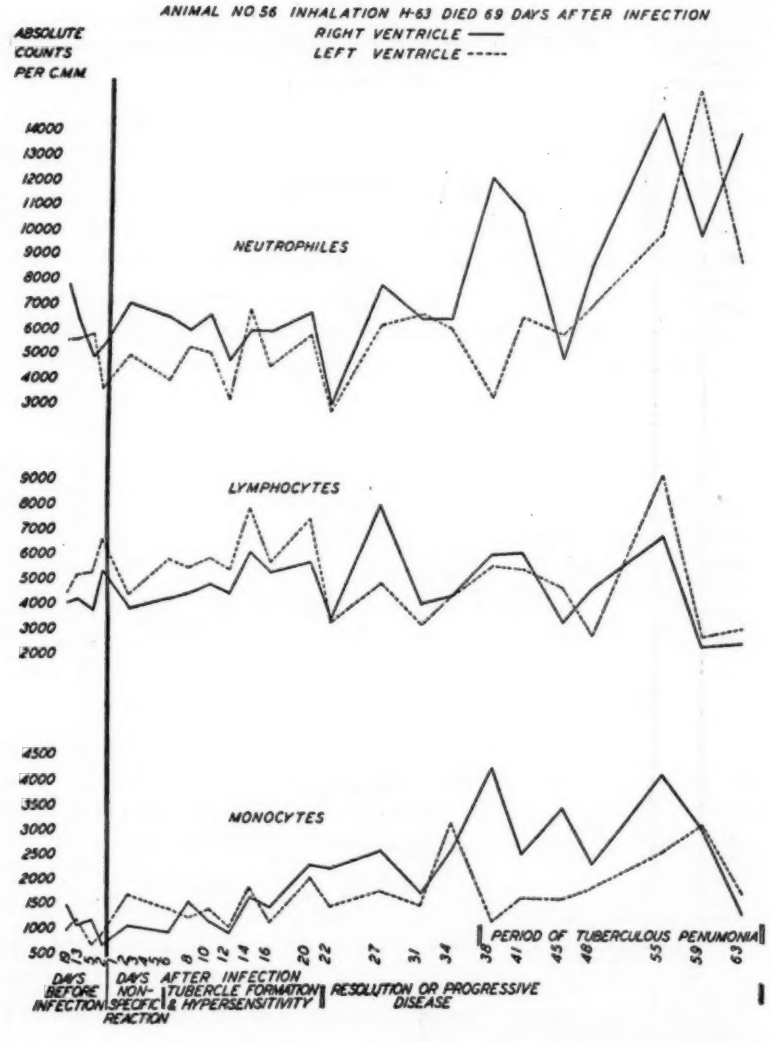


PRESENTATION OF DATA

The different leucocytes of the blood were computed in absolute numbers. On charts I, II, and III, graphs for each class of white

cells in both ventricles are plotted for three representative animals. Animals 52 and 56 were infected by inhalation of the virulent strain H_{63}, and animal 2 by intratracheal inoculation of a large dose of attenu-

CHART II

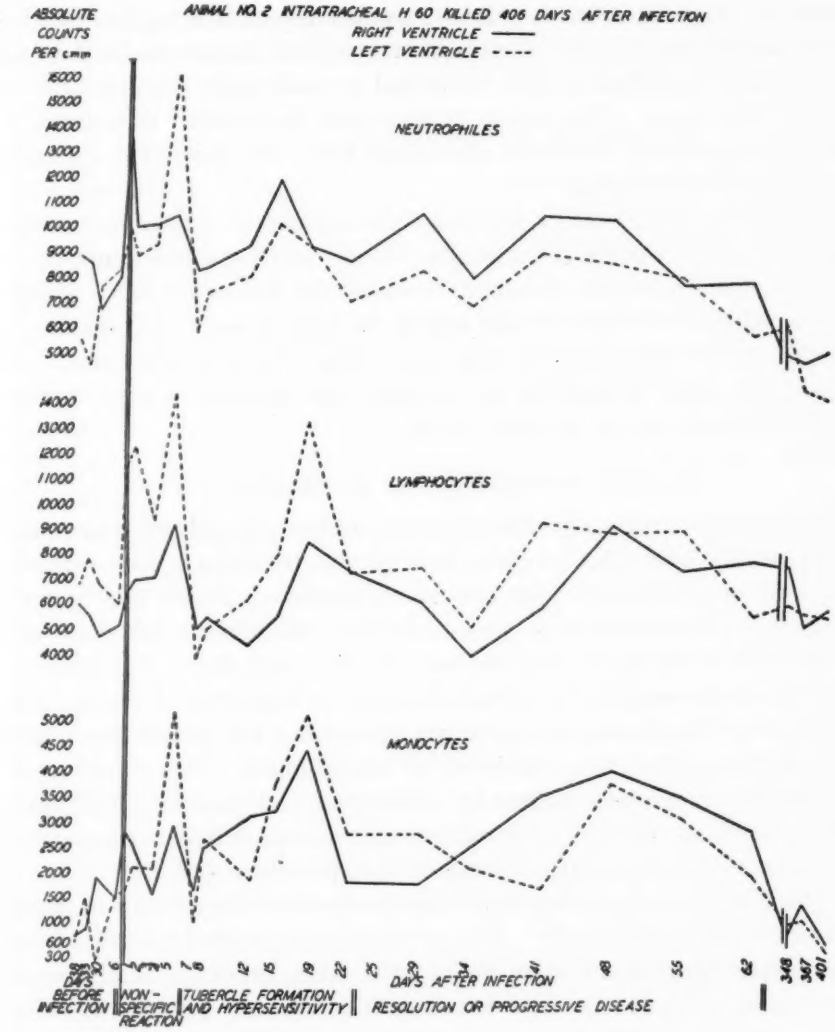


ated strain H_{60}. Space does not permit reproduction of the findings in other animals but in a general way they are similar to the examples shown.

EXPERIMENTAL FINDINGS

A study of the curves seems to indicate that peak reactions for different types of leucocytes occur in more or less orderly sequence. The

CHART III



intensity and duration of the different responses depend upon the variable factors of resistance, dosage, and virulence, but the trends can be identified and they have recurred with sufficient regularity in the differ-

ent types of infection studied to make it appear that they reflect pathological tissue reactions.

NONSPECIFIC REACTION

Blood counts during the first 4 days: Within one to eight hours after infection there is, in most animals, an increase of neutrophiles in the right ventricular blood. These cells reach their maximum in the 5th or 8th hour and then subside to normal or moderately increased levels at the 24th hour. The one hour and eight hour count of animals 2 and 52 respectively illustrate this initial rise. No qualitative changes in the cells were noted.

Beginning at the 5th or 8th hour, the monocytes appear in increasing numbers in the right ventricular blood, reaching a maximum at 24 hours. They fall again to normal levels on the 2nd or 3rd day. There is a consistent retention of this cell in the lung of most of the animals at this time. Except for an impression that the monocytes may exhibit an increase of motility at this time they differ in no respect from those observed in the normal animal.

TUBERCLE FORMATION AND HYPERSENSITIVITY

Fifth to 21st day counts: The monocyte and neutrophile play the chief rôles at this time; the lymphocyte begins to participate only towards the end of the period. At the start, monocyte production is most marked. The discharge of these cells into the effluent blood is well illustrated in the heavy intratracheal infection with H_{60}. There is only a moderate increase in the animals infected by inhalation of H_{63} and R1. The rise of the monocytes continues throughout the period and peaks are established for this cell in all of the animals. The monocyte is functionally active as indicated by the increase and irregular distribution of the vacuoles, but it is still recognizable as an adult blood monocyte and has none of the characteristics of the epithelioid cell.

There is a rise of neutrophiles in all groups with the animals in group 1 reacting most vigorously. The polynucleosis, no doubt, results from the inflammatory reaction aroused by the extension of the local process into tissue already rendered hypersensitive by the primary nodules. Skin tests made with 0.1 cc. of a 2 per cent solution of Old Tuberculin elicited a four plus reaction in all of the H_{63} animals between the 17th and 24th day.

Qualitatively, many neutrophiles exhibit an increase of the small

orange-stained vacuoles scattered among the streaming granules. Also nonstaining vacuoles, 2 to 3 micra in diameter, appear in some cells. The modified cells are seen in blood from both ventricles and are actively motile. The retention of the cell occurs consistently in all of the animals.

The lymphocytes now increase in most of the animals. A large proportion of the lymphoid cells have lobulated nuclei and some exhibit slow motility.

EXTENSION OR RESOLUTION OF THE DISEASE

Twenty-second to 63rd day counts: At the beginning of this interval there is a tendency for all leucocytes, except the monocyte, to maintain a more or less constant low level. In animal 2 the monocytes decrease to preinfection levels. In the inhalation groups, on the other hand, the monocytes remain at a high level or even continue to increase. Progressive disease with the resulting necrosis explains the monocytic activity in the latter group. The lymphocyte becomes a dominant cellular constituent of the blood in the attenuated H_{60} animals but is depressed in the virulent H_{68} series. The neutrophile does not increase at this time.

The final phases of animals 2, 52 and 56 can best be considered individually for there is a marked contrast in their respective blood pictures. During this period the varying character of the disease is reflected in the behavior of the leucocytes. An animal in the same series with number 2, killed 48 days after infection with attenuated bacilli (chart III), presented an apparent clearing of some of its disease but in many areas there was still a diffuse pneumonic infiltration of monocytes, giant cells, lymphocytes and a few neutrophiles. This histopathology is correlated with a normal neutrophilic count, a moderate rise followed by a fall of the monocytes and a gradually increasing lymphocytic count. Animal 2, which was not killed until 406 days after infection, showed no evidence of tuberculosis in the lungs or spleen but its tracheobronchial nodes were fibrocaseous.

Animal 52 (chart I) died 56 days after infection. The lungs show a moderate number of spreading caseous tubercles. In sections there is well-marked lymphoid hyperplasia with very few neutrophiles. The blood had shown a leucopenia with no relative increase of any of the leucocytes, probably due to the toxic effects of the disease. There is a definite depression of the lymphocyte with no retention of the monocyte.

On the other hand, animal 56, dying on the 63rd day, exhibits high total white counts due to the increase of neutrophiles and monocytes which are being retained in the lung. In this case the histological examination of the lung discloses extensive caseous tuberculosis spreading in pneumonic form from the primary foci. The air spaces are filled with neutrophiles which are reflected in the increased number of these cells in the blood entering the lung. The monocytes are retained in the lungs of this animal, a reaction which will be commented upon in the discussion.

The above mentioned periods in the evolution of pulmonary tubercle seem to be characterized by distinct differences in the composition of the ventricular blood. They are summarized as follows:

1: First four days: (*Nonspecific inflammation.*) There is a marked polynucleosis reaching a maximum from the 5th to the 8th hour and returning to normal average values on the 24th hour. A moderate rise of monocytes is evident on the 8th hour and persists to the 2nd or 3rd day. All types of infection had the same effect.

2: Fifth to 21st day: (*Tubercle formation and hypersensitivity.*) This period is characterized by a rise of monocytes. Both retention and discharge from the lungs occur in individual animals.

Neutrophiles are found in increasing numbers in the right ventricular blood of all animals and the cells are retained in the lung. Toward the end of the period the neutrophiles decrease and the lymphocyte curve rises in the majority of the animals. The blood picture presumably reflects a specific exudative inflammation initiated by the extension of the disease into allergic tissue. Lymphocytic infiltration occurs in its later stages.

3: Twenty-second to 63rd day: (*Extension or resolution of the disease.*) Infection with attenuated strains, H_{60} and R1, produces lesions that subsequently retrogress. The first part of this period is characterized by mononucleosis; its later stages by a high relative lymphocytosis. The neutrophile returns to preinfection levels.

All animals infected with the virulent strain H_{63} died of generalized tuberculosis at this time. Depression of lymphocytes with monocytes and neutrophiles at high levels characterized the blood findings at death.

DISCUSSION AND RESULTS

Comparative ventricular counts offer an approach to the problem of the source of the cellular constituents of the pulmonary tubercle. In spite of the fluctuations in the normal animal, the differences in the number of monocytes in the ventricular blood before and after it passes

through the infected lung are sufficiently significant so that in many instances they can be correlated with the cellular reactions in the pulmonary tissues. The hypothesis that monocytes migrating from the blood-stream are the progenitors of the epithelioid cell postulates an excess of these cells in the blood from the right heart and the demonstration of a consistent retention of these cells in the lung during the phases of active tubercle formation.

But an analysis of the ventricular differences of the monocyte during this period, in a majority of the animals, discloses either fluctuations comparable to those in normal animals or even an excess of monocytes into the left ventricular blood. Therefore, the only conclusion that can be drawn from this study is that epithelioid cells are chiefly derived from cells already in the lung and that occasional surpluses are eliminated in the efferent blood.

Now and then the counts indicate a temporary excess of monocytes in the afferent blood and a retention within the lungs. These instances coincide with or follow a polynucleosis. Such association is noted particularly in animal 2 on the first day, and in animal 56 from the 35th day to its death. The polynucleosis and the retention of the monocyte are usually of a short duration except in cases of tuberculous pneumonia (animal 56). Where this occurs it is probable that many of the monocytes are retained to phagocytose disintegrating and injured neutrophiles. Most of the phagocytic monocytes leave the lung either by the way of the lymphatic vessels or as a bronchial exudate.

It seems probable that the increase in monocytes in the peripheral blood of tuberculous animals is due to cells from two sources; the general circulation and the connective tissues at the site of reaction. Where the stimulus is slight the local elements are adequate to produce enough monocytes; in extensive pneumonic reactions blood cells from distant parts are called into action.

The behavior of the lymphocytes during infection corresponds with the findings of most observers. There is an increase of lymphocytes at the end of the period of tubercle formation when allergy is developing. A lymphocytosis persists in the animals injected with the attenuated strains, while the animals infected with the virulent strain H_{63} show decreasing numbers of the cell. Furthermore, the discharge of the lymphocyte into the left ventricular blood noted in the normal animals continues after infection. Therefore the assumption that cells of this type proliferate in the pulmonary lymphoid tissues and wander into the blood-stream seems justified.

As observed by many investigators, the rise of the neutrophile was the initial cellular response to infection. The reaction usually subsided within twenty-four hours. However, the intensity of the reaction was not always correlated with the number of inoculated bacilli. Animals receiving few bacilli by inhalation often responded with higher totals than the ones which were infected with a heavy dose. A second rise of the neutrophiles occurred with marked retention in practically all of the animals at a period correlated with the development of hypersensitivity. Unlike the prompt early transitory rise, the elevation of the cell is gradual and persists from four to seven days. In retrogressive disease, the neutrophile returned to normal levels, but in animals in which necrosis and caseation appeared, the blood showed continued increase of the cell. Likewise, as indicated in the uninfected animal, the blood loses neutrophiles in passing through the lung.

We are grateful to Dr. L. U. Gardner for his guidance during this study.

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THE ERYTHROCYTE SEDIMENTATION REACTION IN CHRONIC PULMONARY DISEASE[1,2]

ARTHUR B. ROBINS

This study was undertaken in an attempt to investigate the erythrocyte sedimentation reaction in certain chronic pulmonary diseases. The conditions considered were chronic pulmonary suppuration, including lung abscess, carcinoma of the lung, bronchiectasis, silicosis, and pulmonary fibrosis of indeterminate aetiology. No case of chronic pulmonary tuberculosis in which one of the above conditions was not present has been included.

MECHANISM OF SEDIMENTATION REACTION

In any work on sedimentation of the blood, it is of value to consider the state of our present knowledge concerning this phenomenon, its mechanism, and the factors which affect it. The scope of this study does not permit a discussion of the historical background underlying our present-day concepts of blood sedimentation. For this we must refer to the masterly papers of Fahraeus (1) (2). The same author has also clearly analyzed the mechanism of this reaction.

The corpuscles of the blood are particles suspended in a fluid medium of lesser density. As such they are subject to the physical laws governing such systems. These are inherent in Stokes's formula:

$$v = \frac{2}{9} g \frac{S - S_1}{u} r^2$$

in which v = the velocity of fall, g = a gravitation constant, S = the specific gravity of the particle, S_1 = the specific gravity of the fluid, u = the absolute viscosity of the fluid, and r = the radius of the particle. This formula implies that the rate of fall will be directly proportional to the square of the radius of the particle and inversely proportional to the viscosity of the medium.

[1] From the Tuberculosis Service of the First Medical Division of Bellevue Hospital, New York City.

[2] Submitted in partial fulfillment of the requirements for the degree of Doctor of Medical Science, Columbia University.

Of these two factors, the more important is the size of the particle. This is but slightly dependent on the concentration of the corpuscular elements and their diameter. A far more decisive rôle must be assigned to their property of aggregation. Rapid sedimentation is associated with a greater tendency of red cells to clump together in rouleaux, as can readily be observed in the blood of pregnant women. This increased aggregation, or decreased suspension stability, is dependent on alterations in the cell-plasma interface. The normal stability of the red blood corpuscles *in vivo* depends on three forces. The first is the difference in surface tension between cell and plasma, the second is the mutual repulsion manifested by bodies such as red cells possessing similar electrical charges, and the third factor is the influence of the hydrophilic property of the capsule of the red cell in maintaining the stability of the suspension. The greater the tendency to bind water, the more stable the system. These three forces are mutually interdependent, and, in some instances, antagonistic. The way in which they act will be discussed in connection with the factors affecting the sedimentation reaction.

FACTORS AFFECTING THE SEDIMENTATION RATE

These can be grouped in two main categories. In the first are included those factors whose influence is exerted directly upon the components of the blood. Alterations in cell content and characteristics, and differences in constituents of the plasma, fall in this class. The second group consists of those forces which modify the physiological state of the patient and only indirectly affect the elements of the blood. In this category are found such factors as age, menstruation, pregnancy and fever. Although it is obvious that these subdivisions are arbitrary and frequently tend to overlap, we feel the subsequent discussion will be simplified by the use of such a classification.

In our first group we must consider the formed elements of the blood and the plasma. The effect of alterations in red-cell number, diameter, haemoglobin content and oxygenation has been extensively studied. The consensus is that anaemia increases and polycythaemia decreases the erythrocyte sedimentation rate (3) (4) (5) (6) (7). *In vitro* dilution experiments bear this conclusion out (2) (8) (9) (10) (11) (12) (13) (14). Of the various factors which go to make up the red-cell concentration, cell volume seems the most important. Several workers (3) (13) (14) have constructed tables for the correction of the sedimentation rate in

terms of cell volume. Fahraeus (2) and Westergren (4), however, warn against an attempt at too close mathematical correlation of the two, particularly in cases with marked anaemia. Observations on the effect of variations in oxygen content on red-cell sedimentation have been conflicting and no definite conclusions can be reached as to the significance of such changes (2) (11).

Studies on the relationship between the other formed elements of the blood and the sedimentation rate have been sketchy and inconclusive. VonVarga (5) noted a close parallelism between total white blood count, percentage of young leucocytes and the speed of sedimentation. The lymphocyte and monocyte percentage varied with the erythrocyte sedimentation rate (E.S.R.) in inverse ratio. Ernstene (19) observed a similar tendency to simultaneous elevation of white count and sedimentation rate. Others, such as Cherry (10) and Achard, Codounis and Hadjigeorges (20), could find no such constant relationship.

More important than the formed elements of the blood in their influence on the E.S.R. are the constituents of the plasma. The most significant rôle has been almost universally assigned to the plasma proteins (1) (3) (4) (10) (17) (23) (27). Only Pinner, Knowlton and Kelly (21) Aldred-Brown and Munro (22) and Achard, *et al.*, could find no relationship between the sedimentation rate and the protein content. Of the various protein fractions, fibrinogen seems most important (2) (7) (24) (25). This is particularly true in acute infections. In chronic pathological conditions, globulin may play a more decisive part (8). Whether its effect is independent of the albumin content or a resultant of changes in the albumin-globulin ratio, is still a matter of disagreement (6) (10) (24) (26). Albumin appears to inhibit red-cell sedimentation (2) (5). The mode of action of the plasma proteins is unsettled. In addition to the changes in surface tension which they produce, fibrinogen, and particularly globulin, decrease the negative electrical charge of the corpuscles. Both are powerful dehydrating agents and may diminish the stability of the cell suspension through the exercise of this property. Although different observers (6) (10) (17) (18) attribute rôles of varying importance to these mechanisms, it seems most likely that all are involved.

The few observations which have been made on the effect of changes in the blood-sugar level on the sedimentation rate would indicate that red cells sink more rapidly in sugar solutions than in normal citrated plasma, but that the differences are not significant when blood-sugar levels are within physiological limits (10) (18).

Studies on the blood lipoids and the sedimentation rate have given rise to sharply divergent opinions. One worker (28) finds that cholesterol increases and lecithin decreases the rate of red-cell fall. This he attributes to the difference in electrical charge of the two substances. Another (Theorell, quoted by Leffkowitz (8)) claims that both inhibit sedimentation, the increase in rate in the case of cholesterol correlating with the extractable cholesterol fraction. This latter author postulates an adsorption of the lipoids by the red-cell surface, increasing its negative charge. Still others (4) (20) (21) (24) find no relationship between the concentration of these substances and the erythrocyte sedimentation rate.

Greater agreement exists as to the influence of electrocytes on the sinking velocity of the red cells. Linzenmeier (16) Starlinger (17) and Raue (18) have shown that acids, alkalis and salts, irrespective of their ionization, inhibit the fall of the red cells. Raue, who has given this subject the greatest study, has established the order of potency of various acids, alkalis and salts, and their effective concentration. The same author has demonstrated the failure of nonelectrolytes to alter the sedimentation rate. Electrolytes possess the property of causing proteins and their split products to swell. This in turn leads to increased hydration of the cell with consequent augmentation of its stability. In this way the sedimentation of the red blood corpuscles is inhibited.

In our second group, attention must be devoted to those factors which affect the sedimentation rate by altering the physiological state of the individual. The first of these is sex. Differences between the sexes have been noted, the higher normal levels being found in the female (2) (12) (13) (14). This has been attributed to the increased globulin content of the blood plasma in women. Age is another factor of importance. The sedimentation rate is decreased in the first month of life (25) and increased in old age (24). In both cases corresponding changes in fibrinogen content have been observed. During pregnancy marked variations in the speed of sedimentation are found. It may be accelerated as early as the second month (2), and is regularly increased after the third month of gestation (7). This acceleration continues to the end of term and recedes during the puerperium. These changes correlate closely with fluctuations in the globulin and fibrinogen levels. The effect of menstruation is less well established. Some of the earlier workers, notably Fahraeus, and Linzenmeier, believe the E.S.R. is increased during the menses. Cutler in this country and Walton (33)

in England corroborate their observations. Greisheimer, however, could observe no such differences (30). More recently, Bertrand and Rousseaux (31) have detected rhythmic variations in the sedimentation rate during the phases of the menstrual cycle. These they attribute to alterations in blood viscosity produced as a result of endocrine action.

It has been generally assumed that fever increases the rate of fall of the red cells and numerous clinical observations have been recorded confirming this conclusion. Most of these reports have failed to allow for the effect of the underlying cause of the fever. Bernet (29) has studied this problem in dogs in which hyperthermia is readily brought about. By using different methods for the production of an elevated temperature, he was able to show that fever in itself was without influence on the sedimentation rate.

Factors, such as time of day, relationship to ingestion of food, and exercise, etc., do not affect the sedimentation rate (5) (11).

A subject worthy of brief consideration is the effect of variations in the technique and conditions under which the sedimentation test is performed. No attempt will be made to discuss the methods used for its determination. In essence, all consist of the measurement of the rate of fall of the cells in a sample of blood to which an anticoagulant has been added. The observations are made while the solution is suspended in a narrow glass tube. Several factors are involved. The first of these is the anticoagulant used. The sedimentation rate is unaffected by the use of heparin when the rate is close to the normal level (11) (14). Should it be elevated, heparin increases it further (34). Dried potassium oxalate is without appreciable effect on the sedimentation rate (14), whereas citrate solution may slow it (35). The influence of hirudin on the E.S.R. is an unsettled question. Of the above, only heparin and hirudin do not produce shrinkage of the red cells, an important factor in correcting for differences in cell volume. Another condition markedly affecting the determination of the sedimentation rate is the temperature at which the test is performed. At room temperatures (19°–23°C.) the speed of sedimentation is not altered (3) (11) (14) (15). At higher temperature levels, variations in the rate of settling are noted, depending on the changes produced in the plasma proteins (2) (16) (17). The third most important factor is the size and position of the tube. The length of the tube is of little significance provided its internal diameter is between 2.5 and 11 mm. (14). In tubes less than 2 mm. wide, the influence of capillarity must be reckoned

with. Walton (35) considers 6 mm. the optimal diameter. Inclining the tube from the vertical increases the speed of settling greatly. Estimates of the error produced in this way range up to 100 per cent at a 7.5 degree inclination (15) (35).

MATERIAL AND METHODS

This study is based on a series of 57 cases of chronic pulmonary disease observed on the wards of the Tuberculosis Service of Bellevue Hospital, New York City, in 1933, 1934 and 1935. The series is comprised of three types of cases: first, chronic pulmonary suppuration; second, neoplasms of the lung and mediastinum; and, third, chronic pulmonary fibrosis. Several of the cases were complicated by the presence of chronic pulmonary tuberculosis. The observations in these instances have been included in so far as they reflect changes in the nontuberculous process. The term chronic pulmonary suppuration calls for some clarification. It is used to describe an inflammation of the parenchyma of the lung characterized by active suppuration, usually as a result of anaerobic infection. Necrosis of tissue, with abscess-formation, may be present, or the entire process may resolve without obvious evidence of parenchymal breakdown. In the majority of instances, the aetiology is probably the aspiration of foreign material. Bronchiectasis may be present as an underlying causative factor or may result from long-continued suppuration. Forty-five of our cases fall in this group. These can be subdivided clinically into cases of lung abscess, 27 in number; bronchiectasis, of which there are 8; and chronic pulmonary suppuration of an undifferentiated type, 10 in all. Included in this study are 6 cases of neoplasm of the lung, 3 proved by biopsy or autopsy to be carcinoma, and one, lymphosarcoma. The other two cases ran a clinical course and had X-ray findings so consistent with the diagnosis of neoplasm that we have felt justified in including them in this category. The 6 cases of pulmonary fibrosis observed include 4 cases of silicosis in which the diagnosis of a concomitant tuberculosis could not be established by repeated sputum examinations, and two cases of fibrosis of the lung of nonspecific aetiology, probably secondary to chronic upper-respiratory infection.

Two methods for determining the sedimentation rate have been employed. The larger number was studied with the Cutler 1-cc. technique (33). Three per cent sodium citrate was used as an anticoagulant and the results were recorded graphically. A smaller group of cases was

later examined by the method outlined by Wintrobe (12). In this series dry potassium oxalate, 2 mgm. per cc. of blood, was used to prevent clotting. Corrections for red-cell volume were made from the table given by Wintrobe and Landsberg (14). Frequent white blood counts were performed, and the percentage of segmented and nonsegmented forms of polymorphonuclear leucocyte determined in many instances. This was done in an attempt to evaluate the relative merits of various haematological procedures in estimating the progress of the case.

RESULTS

We shall first consider the cases studied by the Cutler method, 36 in all. Twenty-two of these conform to the classical description of abscess of the lung (table 1).

TABLE 1

	MEDICAL TREATMENT	SURGICAL TREATMENT
Acute lung abscess: 14 cases		
Cured	2	2
Improved	1	2
Unimproved	4	0
Dead	2	1
Chronic lung abscess: 8 cases		
Cured	0	3
Improved or stationary	3	0
Dead	1	1

The differentiation of lung abscess into acute and chronic forms has been made arbitrarily, all cases entering the hospital within eight weeks of the onset of pulmonary symptoms being classified as acute. Active suppuration was present in all of these cases at the time of admission to the hospital. Medical treatment has consisted of bed-rest, postural drainage, and bronchoscopy as indicated. The surgical therapy has been incision and drainage, more radical procedures being used only rarely. An abscess is considered cured when all evidence of suppuration has subsided, the patient is afebrile and symptom-free, his expectoration is scant, clear and odorless, and the roentgenogram shows only residual fibrosis. Improvement is characterized by loss of fever and constitutional symptoms, and the presence of slight nonfoul expectoration. Chronic abscesses fall into the category of improved or stationary only when a persistent cavity is unaccompanied by suppuration.

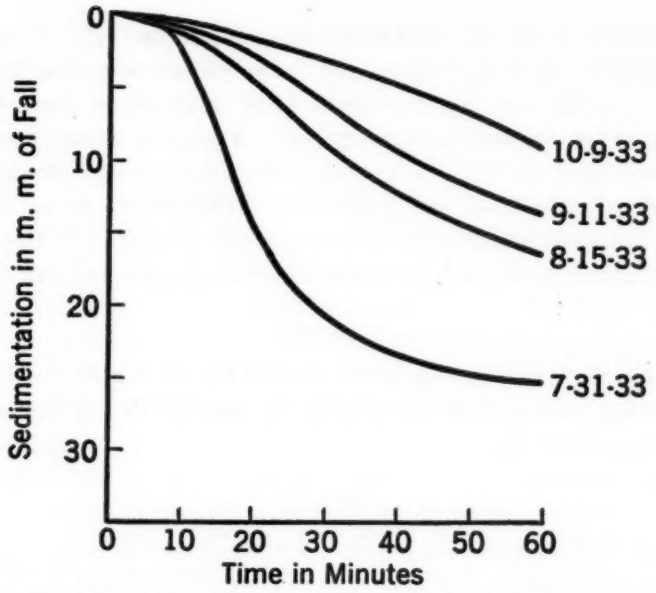

FIG. 1. T. P. Admitted 7/11/33. Lung abscess, 4 weeks' duration. Treatment, postural drainage. Discharged, 10/10/33, cured.

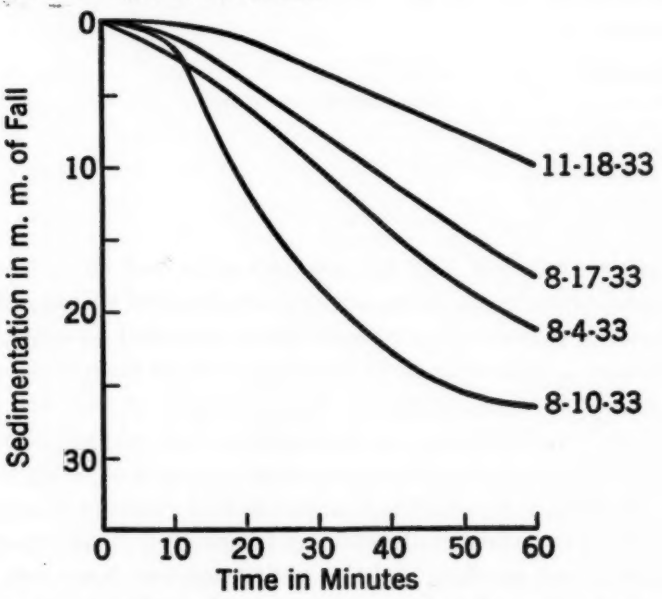

FIG. 2. V. D. Admitted 6/24/33. Lung abscess, 36 hours' duration. Treatment, postural drainage. Relapse, 8/6/33. Incision and drainage, 9/8/33. Discharged 11/22/33, cured.

In the cases of acute lung abscess considered cured, the E.S.R. showed a tendency to shift from a rapid fall at the onset, as portrayed in a vertical curve, to a rate very close to, or within, normal limits. This shift was ordinarily a progressive process from week to week, the horizontal line characteristic of sedimentation in normal individuals being gradually approached. Relapses or extensions were reflected in a shift of the curve back to a more vertical type, as shown in figure 2. The white blood count and polymorphonuclear percentage, always elevated at the onset, reached a normal level long before the E.S.R. Cases 1 and 2 are repre-

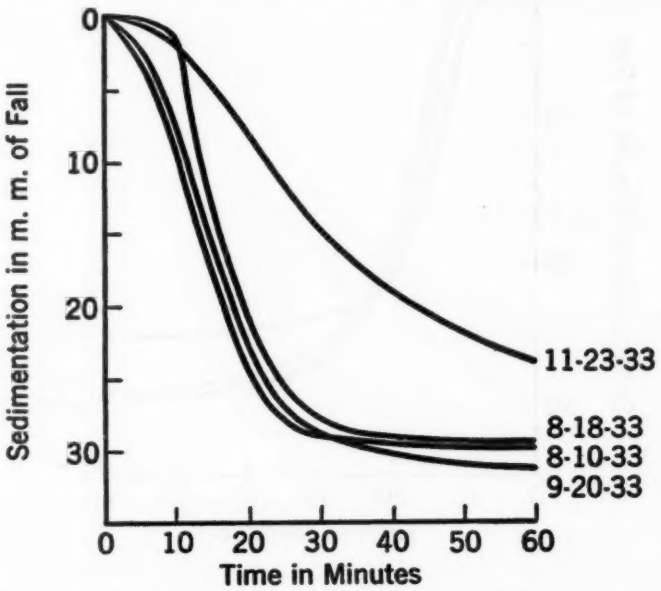

FIG. 3. P. C. Admitted 7/13/33. Lung abscess, 6 weeks' duration. Wassermann ++++. Treatment postural drainage, neosalvarsan, bismuth. No improvement. Incision and drainage, 8/23/33. Discharged, 12/14/33, improved.

sentative of abscesses considered cured, case 1 (figure 1) medically, and case 2 (figure 2) by surgical methods. The other abscesses which healed showed similar changes in their sedimentation graphs (cases 3 and 4). The last case is included as a clinical cure despite the persistence of the moderately elevated E.S.R.

Cases have been placed in the category of improved for one of three reasons. In some the period of observation has been too brief to permit of their being classed as cured. In others improvement has been dependent on the conversion of an acute abscess accompanied by sup-

puration into a chronic abscess free from suppuration. In the third group, the suppurative lesion has cleared in great part, partially by resolution or drainage, and partially by organization. The sedimentation graphs in these cases showed a tendency toward a horizontal line, but normal values were never attained. The changes were quite gradual. Cases 5, 6 and 7 represent examples of each of these types and figure 3 (case 7) is illustrative of improvement by drainage and organization.

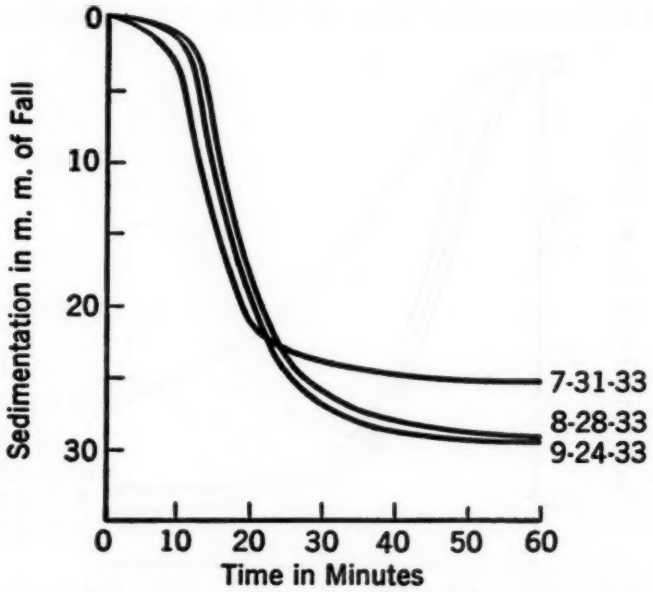

FIG. 4. J. N. Admitted 6/12/33. Lung abscess, 4 weeks' duration. Treatment, postural drainage. Operation advised and refused. Discharged, 10/7/33, unimproved.

The patients who failed to improve showed a striking uniformity in their sedimentation graphs. The rates, which were initially high, tended to remain stationary. Clinically these cases were characterized by the persistence of active suppuration. Operation was repeatedly advised in this group. Cases 8, 9 and 10 show this picture. Case 11 left within ten days of admission and but one reading was obtained. A typical curve is shown in figure 4.

The three fatal cases in this group were characterized by high sedimentation rates. Two died shortly after admission before surgical intervention was possible (cases 13 and 14). The third (case 12) was oper-

ated upon, but adequate drainage could not be maintained. After six operations, the patient developed a subarachnoid haemorrhage and died.

A different type of picture was observed in chronic lung abscess. Here two broad groups must be distinguished. In one, the abscess presented itself as a solitary, fibrous walled cavity unaccompanied by suppuration. Such cases usually represented a late stage in the course of an acute abscess undergoing improvement. The surgical treatment of choice was lobectomy. One of the deaths in this series (case 22) followed such a procedure. The other group consisted of abscesses accompanied by

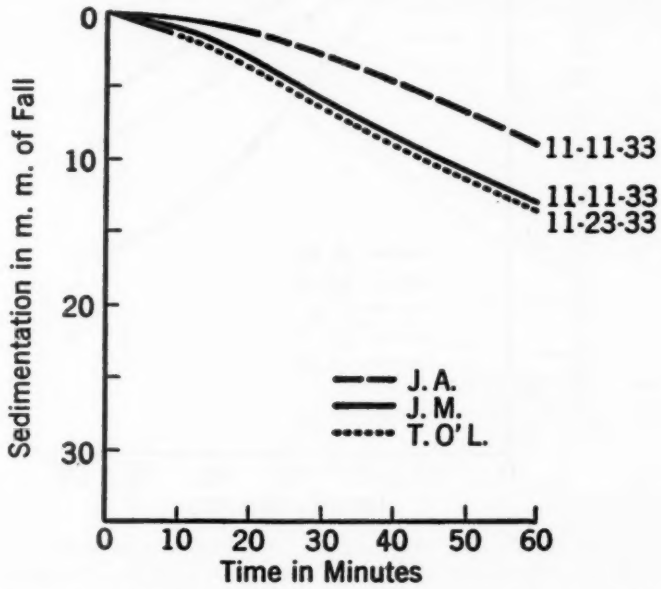

FIG. 5. J. A. Chronic lung abscess. Treatment, postural drainage. Course stationary.
J. M. Chronic lung abscess. Treatment, incision and drainage. Cured.
T. O'L. Chronic lung abscess. Treatment, incision and drainage. Cured.

suppuration. Improvement in such cases occurred by the resolution of the inflammatory exudate. If the process was not of too long standing, a cure could be effected through adequate surgical drainage. The E.S.R. determinations in these patients were a reflection of the extent of the suppuration. In the presence of active inflammation, the rate was always markedly elevated. In improved or stationary cases, in which cavities were unaccompanied by any appreciable degree of suppuration, slightly elevated values were obtained. In healed abscesses, the rates were relatively normal. Figure 5, representing cases 16, 17

and 18, illustrates the type of curve obtained in this last type. Cases 15, 19, 21 and 22, are other examples of chronic lung abscess.

Our series includes three atypical instances of pulmonary suppuration, namely, cases 23, 24 and 25. All three presented evidences of a tuberculous infection, and in two of them, cases 23 and 25, the tuberculosis was active. In the former, the two processes manifested their activity concomitantly; in the latter, tuberculosis became active only after the

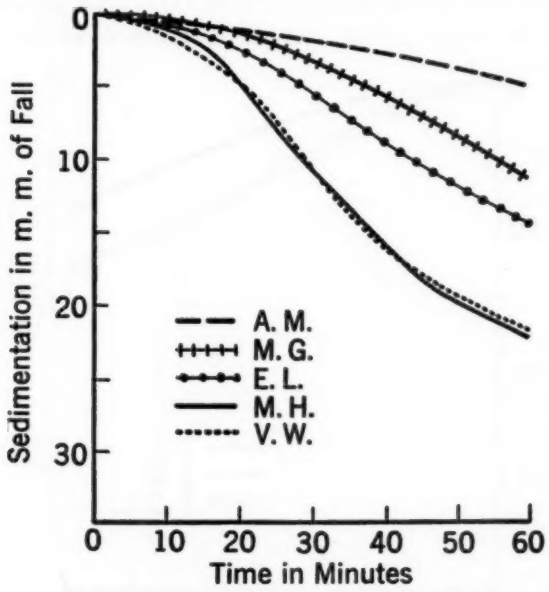

FIG. 6. Case 26. A. M. Dry bronchiectasis. Admitted with haemoptysis.

Case 27. M. G. Tubular bronchiectasis. Slight expectoration. Treatment, artificial pneumothorax.

Case 28. E. L. "Cystiform" bronchiectasis. Surrounding pneumonitis present on admission.

Case 29. M. H. Mixed bronchiectasis. Expectoration and haemoptyses for 28 years.

Case 30. V. W. Saccular bronchiectasis. Surrounding pneumonitis present on admission.

subsidence of the suppurative infection. No conclusion can be drawn as to the significance of the E.S.R. determinations in any of these patients.

As with abscess of the lung, two factors must be considered in cases of bronchiectasis. One is the anatomical deformity, in this case the ectasia of the bronchi; and the other is the attendant inflammatory reaction. These factors were operative in varying proportions. At

one extreme were the cases of so-called "dry" bronchiectasis in which suppuration was minimal. At the other extreme were the putrid bronchiectases with extensive surrounding pneumonitis customarily considered representative of the disease. The E.S.R. varied almost directly with the degree of inflammation present. However, the high levels reached in abscess of the lung were seldom seen. The results obtained

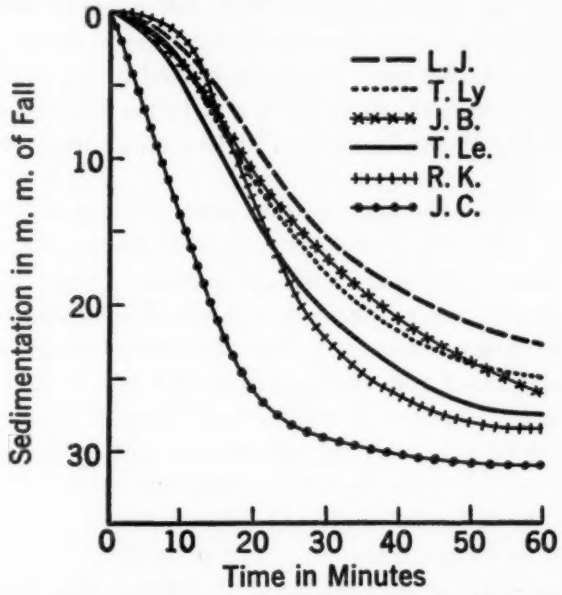

FIG. 7. Case 31. J. C. Carcinoma of left main bronchus with extensive suppuration. Autopsy.

Case 32. T. Le. Carcinoma of right main bronchus. Biopsy.

Case 33. T. Ly. Carcinoma of the trachea at the carina. Autopsy.

Case 34. L. J. Neoplasm of left main bronchus. Progressive involvement of left upper lobe and left lower lobe over 18 months, terminating in death.

Case 35. J. B. Lymphosarcoma, invading right lower-lobe bronchus. Biopsy.

Case 36. R. K. Mediastinal tumor (lymphoblastoma?) giving rise to mediastinal obstruction. Rapid shrinkage following radiation. Recurrence several months later.

in the five cases of bronchiectasis studied are shown in a composite graph, figure 6.

Cases of neoplasm of the lung showed the slightest variations in sedimentation rate. As with new growths elsewhere in the body, the rate was always markedly elevated. The type of neoplasm and its location seemed to make little difference. Tumors of the mediastinum appear to have produced the same effect as those arising from the bronchi.

Extensive suppuration distal to the growth increased the rate somewhat. Figure 7 illustrates our results in this group.

In our hands, the 21 cases studied by the Wintrobe method gave less consistent results. Most of the patients who were not acutely ill or had not bled recently were found to have cell volumes running well above the normal values of 46–47 volumes per cent for males and 42–43 volumes per cent for females. These high cell volumes may be due in part to the polycythaemia accompanying chronic pulmonary disease. The high sedimentation rates noted are related to the correction necessitated by the increased cell volumes and to the higher normal figures obtained with the Wintrobe method (0–10 mm. for males; 0–20 mm. for females).

Of the lung abscesses studied, two were discharged as cured. One (case 37) was observed four days before discharge, nine weeks after admission. His E.S.R. was 25 mm. corrected. Total white cells were 7,480, with 68 per cent polymorphonuclears, of which 42 per cent were nonsegmented forms. The other (case 38) was observed over a three-month period. His E.S.R. declined from 44.5 mm. in one hour to 27.5 mm. in one hour. Leucocyte counts varied from 7,950 to 11,750, with polymorphonuclears between 57 and 64 per cent. The nonsegmented forms never exceeded 10 per cent of the total neutrophiles. The third and fourth cases showed marked clinical improvement. The E.S.R. determinations in the former (case 39) were not consistent with this change, persisting at a level between 44.5 and 49.0 mm. The W.B.C. declined from 16,050 to 8,350. The latter (case 40) represents the conversion of an acute into a chronic abscess with gradual contraction of a thin-walled cavity.[3] This case was first observed when all active suppuration had cleared. At that time his E.S.R. was 30 mm. and his W.B.C. was 7,550 with 72 per cent polymorphonuclears, 15 per cent nonsegmented. Two months later his E.S.R. was 20 mm. The last patient with abscess studied (case 41) had been discharged a short time previously as healed with a normal E.S.R. He returned with increased cough, but no fever or foul sputum. X-ray showed no essential change. Sedimentation rate was 21.5 mm. and white blood count 7,450, of which 54 per cent were polymorphonuclears. The nonsegmented forms constituted 17 per cent. He was discharged shortly afterward as cured.

The 7 cases of chronic pulmonary suppuration studied showed wide

[3] This patient later developed clinically active pulmonary tuberculosis.

variations in their sedimentation rates. To some extent this was a reflection either of the type of disease observed, or of the phase in which the observations were made. Two of the cases were examples of previously inefficient drainage of a lung abscess with subsequent chronic bronchiectasis and suppuration. Both showed slight clinical improvement, one after a secondary operation. Their records are presented in table 2.

TABLE 2

CASE	DATE	E.S.R.	W.B.C.	POLYMORPHONUCLEARS	NONSEGMENTED FORMS
		mm.		*per cent*	*per cent*
42	10/30/34	50	6,950	52	7
	11/12/34	50			
	1/19/35	32	6,950	67	8
43	2/ 4/35	36			
	2/23/35	40			

TABLE 3

CASE	DATE	E.S.R.	W.B.C.	POLYMORPHONUCLEARS	NONSEGMENTED FORMS
		mm.		*per cent*	*per cent*
44	12/ 7/34	38			
	12/21/34	51	14,400	57	23
	Immediately after profuse menstrual haemorrhage:				
	1/19/35	34	9,850	79	9
45	12/ 7/34	47			
	12/21/34	36	15,850	63	11
46	12/21/34	42	8,750	54	15
	2/ 2/35		6,350		
	2/ 4/35	30			

Three other instances of pulmonary suppuration belong in an indeterminate group. All showed improvement; none cleared completely. Table 3 shows the observations made in these cases. One case (no. 47) probably represented a lung abscess complicated by an interlobar empyema. The course was gradually downhill, the patient leaving against advice while still acutely ill. His sedimentation rate varied from 48.5 mm., at its maximum, to 38 mm. at its minimum. At the time of discharge it was 44.5 mm. His white blood count was 12,200, with 75

per cent polymorphonuclears, of which 33 per cent represented young forms. The last patient with pulmonary suppuration (no. 48) was still under observation at the time this paper was written. He represented an instance of lobar pneumonitis, which had manifested considerable clearing but was still undergoing active suppuration. His E.S.R. varied from 28 mm. to 38 mm.; his white count was 8,500.

From our limited observations in this group of cases, few conclusions can be drawn. In this series, as in the one studied with the Cutler method, the E.S.R. seemed to depend on the presence or absence of

TABLE 4

CASE	DATE	E.S.R.	W.B.C.	POLYMORPHONUCLEARS	NONSEGMENTED FORMS
		mm.		*per cent*	*per cent*
49	11/10/34	34	9,680	55	50
50	11/10/34	36	13,440	67	55
51	3/ 2/34	42	8,350	63	16
	3/22/34	35			

TABLE 5

CASE	DATE	E.S.R.	W.B.C.	POLYMORPHONUCLEARS	NONSEGMENTED FORMS
		mm.		*per cent*	*per cent*
52	2/23/35	32	18,450	63	15
53	3/22/35	36	9,650	70	15
54	10/29/34	44.5	9,100		
55	10/29/34	42	8,000		
56	3/14/35	42	16,750		
57	3/11/35	40	15,000	82	24

suppuration. No close relationship existed between the E.S.R. and the total white count, polymorphonuclear percentage or ratio of segmented to nonsegmented forms. The leucocytes tended to be normal more often in the presence of active disease than the sedimentation rate.

The three cases of bronchiectasis showed similar clinical and haematological pictures. All were of the putrid variety and were accompanied by a moderate degree of pneumonitis. Table 4 shows the studies made. The results in this group are in accordance with those expected from our previous studies on bronchiectasis. In the presence of parenchymal suppuration the rates were moderately elevated. The striking finding

was the marked increase in nonsegmented polymorphonuclear leucocytes in cases 49 and 50, and the relatively low percentage of these cells in case 51.

Our last series is composed of 6 cases of pulmonary fibrosis. Four of these were patients with silicosis in whom a positive sputum was never obtained. The other two were cases of pulmonary fibrosis associated with low-grade respiratory tract infection. The findings in all six instances were so similar that we are including them all in table 5. The cases of pulmonary fibrosis were characterized by a relatively high sedimentation rate, irrespective of aetiology. The silicotics suspected of having tuberculosis showed no appreciable difference in rate from the others. In three of the cases the total white count was considerably elevated; in the others, normal. The last case showed an increase in the number of both polymorphonuclear and young forms.

CONCLUSIONS

The results of our studies indicate that the most important factor affecting the sedimentation rate is infection. In suppurative conditions of the lung the rate is always high in the presence of active inflammation, and tends to fall as the inflammatory process subsides. In neoplastic diseases of the lung and mediastinum the rate is further increased when extensive suppuration is present. Only in pulmonary fibrosis are elevated values for the E.S.R. noted in the absence of obvious infection. The mechanism by which the E.S.R. is altered in these conditions is not clearly established. It is presumably through changes in the plasma protein level. Whether these in turn are most closely related to tissue breakdown or toxic absorption from the focus of infection, is a matter of dispute. In tuberculosis, a condition in which the sedimentation reaction has been extensively studied, both points of view have been advanced. Levinson (26) finds that the more destructive forms show a higher E.S.R. than the exudative types in which clinical activity is greater. Friedman (36) feels that the more active infections produce the higher sedimentation rates. In the only large series of cases of chronic nonpulmonary disease reported recently, that of Harvey and Reid (37), the E.S.R. was found to vary in proportion to the severity and extent of the infection. In lung abscess, serial studies, plotted graphically, gave curves very similar to ours. In bronchiectasis the rate was elevated whenever pneumonitis was present. The inference to be drawn from their and our observations is that the

Summary of cases

NUMBER	PATIENT	SEX	AGE	MAX. E. S. R.	MIN. E. S. R.	LAST E. S. R.	TEMPERATURE	MAX. W. B. C.	POLYMORPHONUCLEARS, PER CENT	DIAGNOSIS	RESULT AND TREATMENT
1	T. P.	M	43	27.5C	9.0	9.5	98.6	18,800	82	Lung abscess, acute	Cured; med.
2	V. D.	F	26	26.5	10.0	10.0	98.2	15,250	84	Lung abscess, acute	Cured; surg.
3	A. D.	M	45	33.0	7.5	7.5	98.0	24,000	85	Lung abscess, acute	Cured; med.
4	D. McN.	M	33	31.0	19.0	19.0	99.2	17,400	70	Lung abscess, acute	Cured?; surg.
5	M. S.	M	40	26.0	10.0	10.0	98.2	22,350	74	Lung abscess, acute	Imp.; med.
6	A. S.	M	23	31.5	31.5	31.5	101.0	—	—	Lung abscess, acute	Imp.; surg.
7	P. C.	M	44	31.5	22.5	24.0	99.0	18,600	75	Lung abscess, acute	Imp.; surg.
8	J. N.	M	44	29.0	11.5?	29.0	98.8	26,000	61	Lung abscess, acute	Unimp.; med.
9	S. G.	M	42	27.0	16.0	17.5	98.8	19,500	83	Lung abscess, acute	Unimp.; med.
10	J. A.	M	50	31.5	23.0	23.0	98.0	10,200	69	Lung abscess, acute	Unimp.; med.
11	B. S.	M	34	28.0	28.0	28.0	99.2	14,050	66	Lung abscess, acute	Unimp.; med.
12	R. W.	M	34	21.5	21.5	21.5	103.0	22,800	—	Lung abscess, acute	Died; surg.
13	A. K.	M	52	31.0	31.0	31.0	100.4	13,280	77	Lung abscess, acute	Died; med.
14	A. W.	M	53	33.0	33.0	33.0	102.0	18,600	81	Lung abscess, acute	Died; med.
15	J. H.	M	61	34.0	34.0	34.0	98.8	15,700	78	Lung abscess, chronic	Died; med.
16	J. A.	M	26	10.0	9.0	9.0	99.0	12,000	56	Lung abscess, chronic	Stat.; med.
17	J. M.	M	43	20.0	13.0	13.0	98.8	7,900	70	Lung abscess, chronic	Cured; surg.
18	T. O'L.	M	37	27.5	12.5	13.5	98.2	23,260	92	Lung abscess, chronic	Cured; surg.
19	F. M.	M	53	32.0	7.5	8.5	100.0	19,800	75	Lung abscess, chronic	Imp.; med.
20	P. F.	M	40	25.0	25.0	25.0	—	9,100	44	Lung abscess, chronic	Stat.; med.
21	T. McL.	M	25	5.0	5.0	5.0	—	—	—	Lung abscess, chronic	Cured; surg.
22	M. S.	M	24	8.5	8.5	8.5	98.2	18,600	80	Lung abscess, chronic	Died; surg.
23	E. W.	M	50	20.0	16.0	16.0	—	8,000	80	Pulmonary suppuration & tbc.	Imp.; med.
24	E. M.	M	56	14.5	14.5	14.5	99.8	12,350	76	Pulmonary suppuration & abscess?	Imp.; med.
25	J. M.	M	57	33.0	25.0	25.0	100.2	7,350	70	Pulmonary suppuration & tbc.	Active tbc.

26	A. M.	M	23	18.0	5.0	5.0	100.0	—	—	Bronchiectasis; haemoptysis; dry	Imp.
27	M. G.	F	19	12.5	9.5	9.5	99.2	—	—	Bronchiectasis; pneumothorax	Imp.
28	E. L.	M	61	14.0	14.0	14.0	—	14,850	82	Bronchiectasis; pneumonitis	Sl. imp.
29	M. H.	M	57	22.0	22.0	22.0	99.6	—	—	Bronchiectasis; haemoptysis	Sl. imp.
30	V. W.	M	26	24.0	16.0	19.0	—	15,600	51	Bronchiectasis; pneumonitis	Sl. imp.
31	J. C.	M	70	31.0	31.0	31.0	101.4	20,700	84	Carcinoma left main bronchus	Died—autopsy
32	T. Le.	M	44	27.5	27.5	27.5	98.4	16,000	78	Carcinoma right main bronchus; biopsy	Unimp.
33	T. Ly.	M	44	27.5	23.0	23.0	99.6	—	—	Carcinoma left & right main bronchus	Died—autopsy
34	L. J.	M	70	22.5	22.5	22.5	98.6	11,400	72	Neoplasm left main bronchus	Died
35	J. B.	M	46	27.0	26.5	27.0	99.4	14,300	91	Lymphosarcoma, right lower lobe bronchus	Unimp.; biopsy
36	R. K.	F	31	28.5	28.5	28.5	101.0	7,800	86	Tumor mediast. (blastoma?)	Unimp.
37	S. B.	M	40	25.0W	25.0	25.0	98.8	7,480	68	Lung abscess, acute	Cured; med.
38	A. S.	M	44	44.5	23.5	27.5	98.8	13,300	56	Lung abscess, acute	Cured; med.
39	D. M.	M	45	47.0	44.5	46.0	—	16,050	—	Lung abscess, acute	Imp.; med.
40	C. D.	M	23	34.0	20.0	20.0	97.4	8,450	78	Lung abscess, acute	Imp.; med.
41	J. K.	M	40	21.5	21.5	21.5	99.0	7,450	54	Lung abscess, healed	Imp.; med.
42	C. B.	M	40	50.0	32.0	32.0	99.4	6,950	67	Pulmonary suppuration, chronic	Imp.; surg.
43	W. T.	M	36	40.0	36.0	40.0	99.2	—	—	Pulmonary suppuration, haemoptysis	Unimp.; med.
44	L. N.	F	30	51.0	34.0	34.0	98.0	14,400	57	Pulmonary suppuration, chronic	Sl. imp.; med.
45	P. R.	M	43	47.0	36.0	36.0	100.0	15,850	52	Pulmonary suppuration, tbc.	Imp.; med.
46	C. McD.	M	37	34.0	30.0	30.0	99.6	8,750	46	Pulmonary suppuration, chronic	Imp.; med.
47	P. L.	M	34	48.5	38.0	44.5	99.0	12,200	76	Lung abscess & empyema	Unimp.; med.
48	D. S.	M	38	28.0	38.0	38.0	100.2	8,500	—	Pul. suppur., chronic	Imp.; med.
49	A. B.	M	19	34.0	34.0	34.0	98.0	9,680	56	Bronchiectasis	Imp.; med.
50	P. H.	M	64	36.0	36.0	36.0	99.0	13,440	67	Bronchiectasis	Imp.; med.
51	A. F.	M	39	42.0	35.0	35.0	98.4	8,350	55	Bronchiectasis; pneumonitis	Imp.; med.
52	M. H.	M	50	32.0	32.0	32.0	98.4	18,450	63	Silicosis	Unchanged
53	W. K.	M	47	36.0	36.0	36.0	99.2	9,650	70	Silicosis	Unchanged
54	A. S.	M	44	44.5	44.5	44.5	98.0	9,100	—	Silicosis	Unchanged
55	A. K.	M	49	42.0	42.0	42.0	98.8	8,000	—	Silicosis; pneumothorax	Unchanged
56	E. Y.	M	52	42.0	42.0	42.0	—	16,750	—	Chronic pul. fibrosis	Unchanged
57	F. A.	M	41	40.0	40.0	40.0	99.8	15,000	83	Chronic pul. fibrosis	Unchanged

C = Cutler method. W = Wintrobe method.

extent of tissue destruction is the factor most responsible for changes in the sedimentation rate in both these conditions. In silicosis, Harvey and Reid, and Bianchi (38), who has studied 21 cases of silicosis with the sedimentation reaction and the Schilling-Arneth leucocyte index, found normal values in uncomplicated cases. When tuberculosis was present the rate was increased. We are at a loss to account for the uniformly high results in our series. One explanation, which presents itself, is the possibility that a greater degree of infection existed in these cases than our clinical and roentgenological studies would seem to have indicated. The oft-noted fact that the development of a mild respiratory infection may necessitate the hospitalization of a patient with pulmonary fibrosis would lend weight to this hypothesis.

As regards the comparative value of the E.S.R. and the blood count in the study of chronic nontuberculous pulmonary disease, our results are too inconclusive to permit of any very definite decision being reached. No correlation between the E.S.R. and the total leucocyte count, percentage of polymorphonuclears, or ratio of segmented to nonsegmented forms could be observed. When a certain degree of parallelism existed, the sedimentation reaction appeared to be the most sensitive index.

In conclusion, it is our opinion that the erythrocyte sedimentation reaction is a valuable laboratory procedure when used in conjunction with X-ray and clinical examination in the study of chronic pulmonary disease. It appears to be of little diagnostic significance, but may be of great aid in estimating the progress of the case under observation. Its prognostic import remains in doubt.

SUMMARY

1. A survey of the literature indicates that the erythrocyte sedimentation reaction (E.S.R.) is a complex physicochemical phenomenon dependent principally on the cell-plasma interface.

2. In the opinion of most observers alterations in the plasma proteins are the most important factors affecting it.

3. In a series of 57 cases of chronic nontuberculous pulmonary disease, the erythrocyte sedimentation reaction was found to vary with changes in the clinical state of the patient.

4. The variations seemed to parallel the extent and severity of the infectious process as manifested in the inflammatory reaction produced.

5. Comparative studies of the E.S.R. and total white count, poly-

morphonuclear percentage, and ratio of segmented to nonsegmented forms, would indicate that the sedimentation rate is the most sensitive index of the clinical course.

6. The erythrocyte sedimentation reaction is a valuable laboratory aid in evaluating the progress of a case of chronic pulmonary disease.

We wish to express our thanks to Mr. Myron Herman for his technical assistance in the preparation of this paper.

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BLOOD CHANGES FOLLOWING CONTINUOUS DAILY ADMINISTRATION OF VITAMIN C AND ORANGE JUICE TO TUBERCULOUS PATIENTS[1,2]

MOLLY RADFORD, EUGENE DE SAVITSCH AND HENRY C. SWEANY

At a previous meeting of this Association, one of us (E. de S.) reported on the "Influence of Orange Juice on Experimental Tuberculosis in Guinea Pigs." The work was first undertaken to determine whether or not the peculiar resistance of rats to tuberculosis (1) (2) (3) was in any way correlated with their ability to "manufacture" their own vitamin C (4) (5) (6).

Several investigators (7) (8) (9) have reported that vitamin C increases resistance of animals to tuberculosis, while one, Bella (10), reports that no protection against tuberculosis could be given to guinea pigs by orange juice or vitamin C. Grant (11), McConkey and Smith (12), Bauke (13), as well as many others (14) to (19), have reported on the increased susceptibility of animals and patients to tuberculosis in the presence of scurvy. J. A. Höjer (20) did rather an extensive piece of work about twelve years ago on both animals and human beings along this line, from which he concluded among other things that (in tuberculosis) "The appetite may diminish so that a sufficient dose of antiscorbutic is not consumed. The conditions of the intestines may become changed so that the consumed dose of antiscorbutic is prevented from having an effect." And again, "Experiments on a larger scale are desirable especially in regions, where, like in the northern provinces of Sweden, the fresh vegetables are as rare as the tuberculosis is frequent." Lastly: "From a therapeutic point of view it may be said that my investigations suggest the importance of supplying a sufficient fully protective antiscorbutic dose to persons in whom the healing of a tuberculous process is aimed at . . . it may in dubious cases be recommended

[1] From the Department of Physiology of the University of Chicago in coöperation with the Municipal Tuberculosis Sanitarium of the City of Chicago. Work done under research grant from the California Fruit Growers Association. Grant administration by Professor A. J. Carlson.

[2] Presented at a session of the Pathological Section, 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

rather to give a little too much than too little of suitable antiscorbutic articles of food."

Our present work is concerned with an attempt to enhance the resistance of tuberculous patients by giving them a superabundance of vitamin C.

One hundred and eleven tuberculous patients with far-advanced, and generally fibroid tuberculosis, under sanatorium care, were selected. These received no other therapy than routine rest. After minute study of all possible aspects of these cases, they were matched up in sets of three patients each which were as nearly comparable as possible; the one having the lowest letter in the alphabet to be reserved as control, the second lowest to receive orange juice, and the third to receive vitamin C in its pure crystalline form. In this evaluation of comparable

TABLE 1

Average determinations at beginning of experiment

	VITAMIN	ORANGE	CONTROL
Fibrinogen	0.546	0.522	0.55
A/G	1.33	1.52	1.44
P/L	3.17	2.84	2.86
Lymphocytes	24.5/100 cells	26.4	27.5
L/M	5.64	4.99	4.57
R.B.C.	4.87 millions	4.96	4.94
Hb	67.0	71.0	69.3
Sedimentation rate	16.9 mm. in 30 minutes	15.2	18.0
Schilling	0.689	1.045	0.688
Weight	118.8 lbs.	120	122.7

cases, age, sex, race, and size were considered carefully. In addition, the extent and type of lung lesions, as judged by X-ray, physical findings, temperature, pulse, and complications were compared. For more objective data, laboratory findings, including complete blood cytology and significant blood chemistry, were recorded and balanced one against another. Hence, in the three large groups resulting, each patient had a counterpart in each of the other groups. There was a parallelism in the average combined figures of the three groups that reveals a high degree of accuracy in the selection and matching of the patients. (See table 1.)

As might be expected, we were not able to keep the original group intact throughout. By the end of the first three months there were 70 patients left, some dying, a number discharged, and others taken off

the treatment for one reason or another. The losses, however, were about equally divided among the three groups. There were eleven lost from the vitamin group, fourteen lost from the orange group, and sixteen from the control group. Because of these losses fifteen new patients were added to fill some of the vacancies, after being carefully matched as before. The nine-month determinations on these added patients is necessarily not included in this report. In the ensuing months fourteen

TABLE 2

Synthetic orange juice

	PER CENT
Buffer mixture:	
Calcium phosphate: $CaHPO_4 \cdot 2H_2O$	1.075
Calcium citrate: $Ca_3(C_6H_5O_7)_2 \cdot 4H_2O$	4.57
Sodium phosphate: Na_2HPO_4	3.83
Citric acid: $C_6H_8O_7 \cdot H_2O$	59.08
Sodium citrate: $Na_3C_6H_5O_7 \cdot 2H_2O$	12.75
Corn starch	18.62
Sunset yellow	0.05
Orange extract:	
Orange oil (five-fold concentrated)	4.57
Alcohol, 95 per cent	95.43
Combine 74 gm. of buffer mixture with 396 gm. sugar, plus 5 cc. of orange extract with sufficient water to make one gallon of beverage.	
Composition of beverage:	
Sucrose	10.10
Anhydrous citric acid	1.017
Orange oil	0.0049
CaO	0.032
P_2O_5	0.044
Vitamin-A content of orange oil used amounts to less than one-third that in same amount of fresh orange juice.	

more patients have been lost from the groups. Hence, the results reported here are actually those for a period of three months on 85 patients, for a period of six months on 71 patients, and for nine months on 56 patients.

The patients were treated as follows: Those in group 1 received 500 cc. of freshly prepared orange juice given in two doses of 250 cc. a day. Patients in group 2 received 500 cc. of a synthetic orange drink

(see table 2) as nearly approaching real orange juice in appearance, smell, taste, and chemistry as possible, to which was added 250 mgm. of crystalline vitamin C. Group 3 received the same amount of the synthetic drink with no vitamin C added.

This treatment to be continued daily for a period of at least one year has been under way for nine months at the time of this report. All observations and examinations on patients have been repeated at inter-

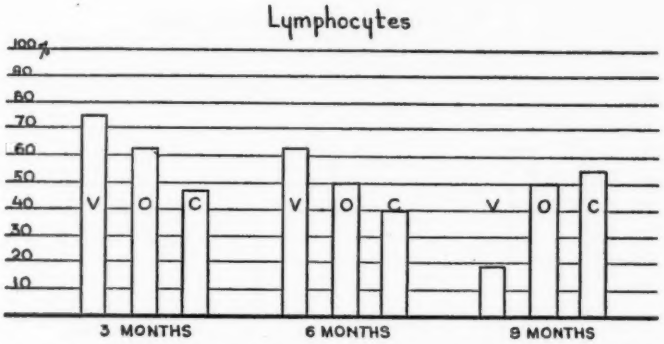

CHART 1. Percentage of patients showing improvement in lymphocytes

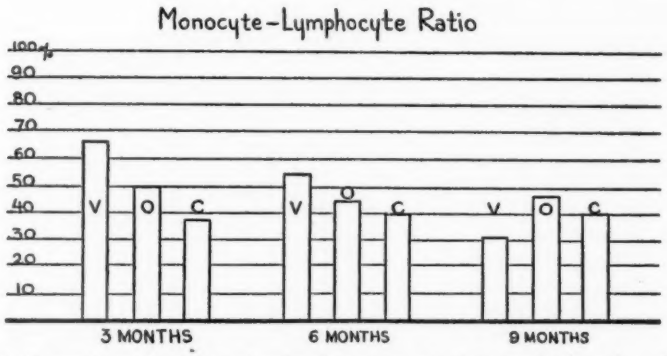

CHART 2. Percentage of patients showing improvement of monocyte-lymphocyte ratio

vals of not greater than three months throughout the experiment. Haemograms were kept on each patient, as in chart 11, to show the progress at a glance. Standard sanatorium diets have not been altered in any way.

Nine different blood determinations were made which were used as indicators of improvement (21) (22) (23). Each determination was taken at the beginning of the experiment, and after three, six and nine

months on each patient. These determinations were expressed in terms of the percentage above or below an arbitrary normal taken from accepted standards. Using the first calculated figure as a starting point, the percentage above or below this was used as an expression of improvement or failure for the subsequent months. As may be inferred from the type of patient used, there was an extensive unfavorable deviation from the normal at the beginning of the experiment. The

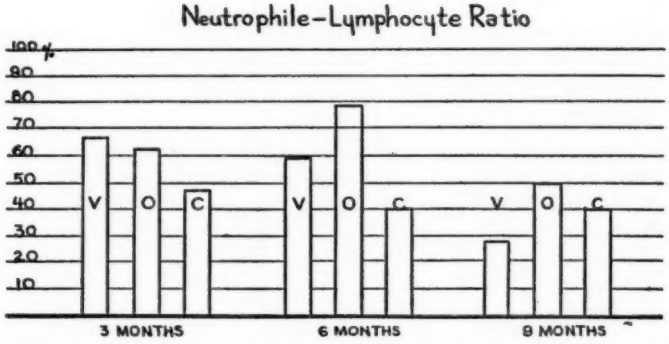

CHART 3. Percentage of patients showing improvement in neutrophile-lymphocyte ratio

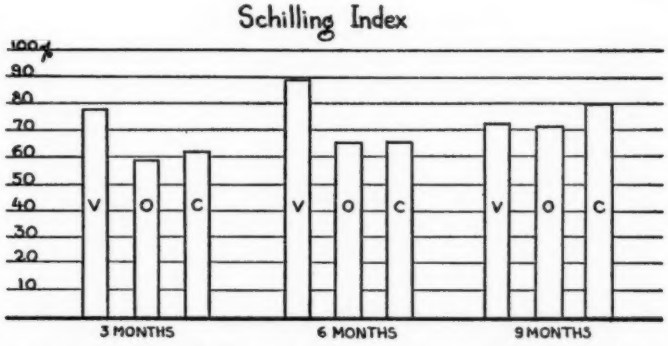

CHART 4. Percentage of patients showing improvement in Schilling index

patients holding their own or improving were grouped together as opposed to those showing a regression. The percentage of patients in each group showing an improvement or a stationary course are charted for three, six, and nine months respectively in charts 1 to 9 inclusive. Chart 10 is a composite of the percentages shown on the other nine.

This report is limited to the laboratory findings, especially to the haematology, as we do not feel that sufficient time has elapsed to allow

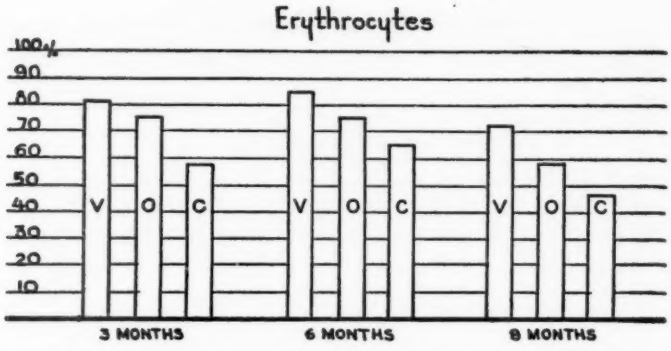

CHART 5. Percentage of patients showing improvement in red-cell count

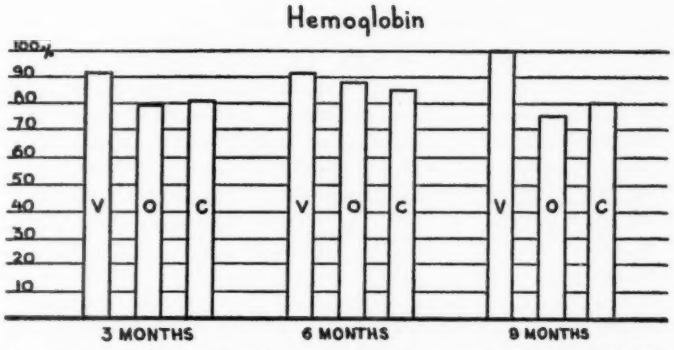

CHART 6. Percentage of patients showing improvement in haemoglobin

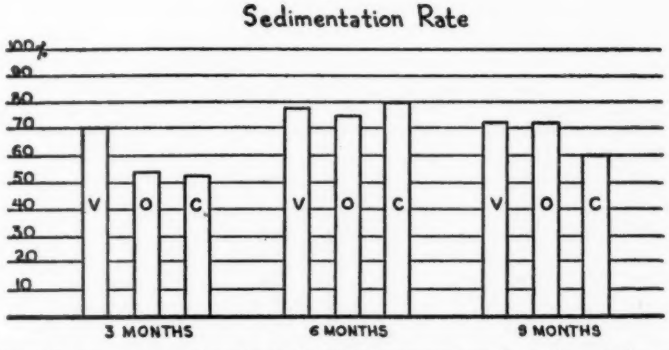

CHART 7. Percentage of patients showing improvement in sedimentation rate

conclusions to be drawn with respect to the X-ray pictures and physical findings. The relation of the haematological picture to clinical progress in tuberculosis has been thoroughly studied (Medlar (24), Sabin (25),

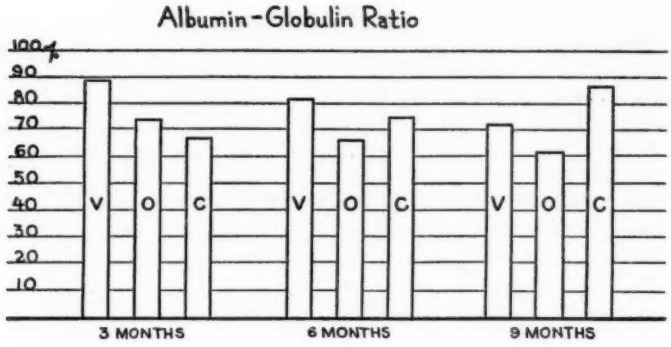

CHART 8. Percentage of patients showing improvement in A/G ratio

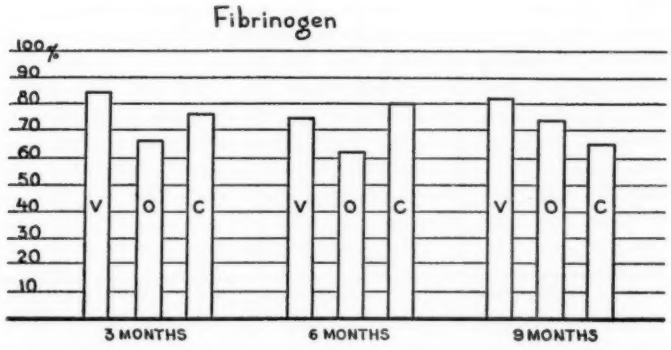

CHART 9. Percentage of patients showing improvement in fibrinogen

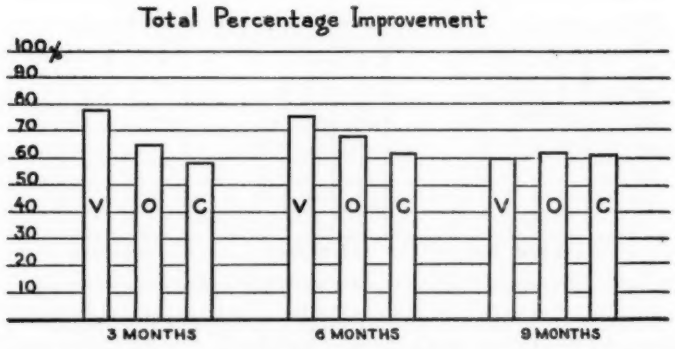

CHART 10. Total percentages of patients showing improvement in the nine blood determinations

Wiseman (26), and others (27) to (32)), and is quite well understood at the present time. Although none of the criteria are of any absolute

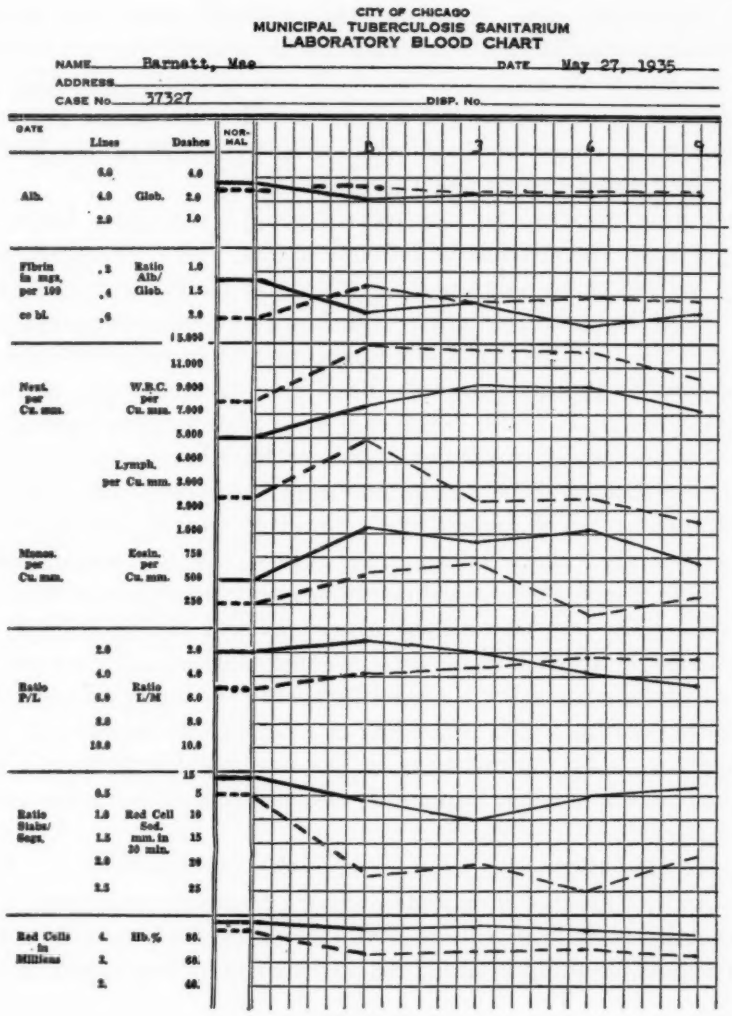

CHART 11. Haemogram of patient

value, we feel that the sum-total of all such findings may be said to be indicative of the true clinical condition of the patient.

As may be seen in the accompanying charts, at the end of the first three months of the experiment, of the patients treated with crystalline

vitamin C, and those treated with orange juice, a definitely greater percentage showed a favorable course, as judged by red blood cell count, haemoglobin, lymphocytes, monocyte-lymphocyte ratio, and neutrophile-lymphocyte ratio, than did the controls. Also the albumin-globulin ratio appeared more favorable in the treated groups at this time.

At the end of six months of this daily administration of orange juice and vitamin C, there was still a notable difference in the percentage showing improvement in blood cytology as well as in haemoglobin between the treated groups and the controls.

After nine months the two treated groups still show better percentages than the controls in red cell counts, and they compare favorably in respect to sedimentation rates and blood fibrinogen at this time. The orange-treated group still shows a greater percentage of improvement in the neutrophile-lymphocyte and monocyte-lymphocyte ratios than do the controls, and the vitamin-treated group persists in showing a definitely better percentage of improvement in haemoglobin. The other findings after this time, however, have become quite negative.

It is too soon to draw conclusions from this work. Because of the far-advanced type of patient used, however, any improvement, even though it be slight, may be interpreted as favorable, and would no doubt bring about a more pronounced favorable effect in patients with a better prognosis. The fact that all the figures reveal a favorable trend after three months, which still persists in some measure after six months, is worthy of consideration. Especially should the study be applied to a type of patient for which something of a permanent improvement may be expected. The improvement in the haemoglobin and red-cell figures indicates a possible haematinic effect that merits further investigation.

We feel that the methods of control of these groups have been highly satisfactory. The system adopted offers a means of conducting a clinical experiment in tuberculosis that eliminates the personal factor as much as possible and practically reduces the results to a numerical basis.

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CALCIFIED LESIONS OF PRIMARY TUBERCULOSIS IN THE INTESTINE IN ADULTS[1]

HENRY W. FERRIS

It is widely recognized that the tubercle bacillus may enter the body through the intestinal wall, and tuberculous infection of the mesenteric lymph nodes, in the absence of other foci of tuberculosis, is generally accepted as evidence of this route of entry. The lesions in the lymph nodes may consist of tubercles, areas of caseation or of calcification with fibrosis. In the great majority of instances, no lesion of the intestine itself is recognized. There are two possible explanations for its absence. The tubercle bacillus may have passed through the wall of the intestine without producing any lesion, or, what is more probable, have caused a small superficial caseous focus that has sloughed off. In that case the ulcer may have healed with no recognizable scar.

In favor of the second view is the occasional finding of ulcers of the intestine, with or without associated tuberculous lesions of the mesenteric lymph nodes, in individuals having no other evidence of tuberculosis. The occurrence of most of these lesions in children supports the opinion that they are primary infections. Beitzke (1) reported the results of a careful study of 1,100 autopsies. He found 13 cases which he considered examples of primary intestinal tuberculosis. He accepted only those in which there was microscopic evidence of the nature of the lesion, or positive results from animal inoculation. In three instances there were small ulcers in the intestine, in two cases without associated lesions of the mesenteric lymph nodes. The remaining 10 cases presented caseation or calcification of the lymph nodes, without intestinal lesions. Eight of the 13 cases were in children and 5 in adults.

Among 714 individuals dying of diphtheria, Heller (2) at the Pathological Institute at Kiel found 140 instances of tuberculosis. In two of these he saw lesions which he believed were examples of primary intestinal tuberculosis. In 8 other cases the mesenteric lymph nodes as well as the intestines were involved. Wagener (3) in 410 autopsies encoun-

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tered 20 cases in which he thought there was evidence of primary intestinal tuberculosis.

Leonard (4) reviewed 161 autopsies performed on children under 15 years of age at the New Haven Hospital. In 50 there was evidence of some form of tuberculosis. In 18 the mesenteric lymph nodes were the only sites of tuberculosis in the body, though on the other hand there were only 5 patients with tuberculosis who did not give evidence of involvement of these nodes. Of the 45 cases with lesions in the mesenteric nodes, intestinal lesions were demonstrated in only about one-third. This observation the author believed supports the opinion that the tubercle bacillus may pass through the intestinal wall, leaving no demonstrable lesion, and lodge in the mesenteric nodes where a focus of infection is set up.

In 1935 Blacklock (5) at the Royal Infirmary for Sick Children in Glasgow studied autopsies made on 2,500 infants and children up to 13 years old. There were 372 in which tuberculous lesions were found. Of these, 123 were believed to be instances of primary abdominal infection. Intestinal ulceration, with caseous mesenteric lymph nodes, was present in 22 cases, while in the remaining 101 autopsies the lymph nodes were involved but no gross lesions were seen in the intestines.

Other reviews of series of autopsies, or single case-reports, present strong evidence that the tubercle bacillus, at least in many instances, produces a lesion in the intestine at its site of entry and in turn causes changes in the associated mesenteric lymph nodes. Recently Reichle (6) has critically reviewed the literature and tabulated the observations which he considered most significant. In many cases, particularly in adults, no intestinal ulcer can be found, and the only evidence of the sequence of events is calcification, with or without associated caseation, of the mesenteric lymph nodes. If primary intestinal tuberculosis has healed, some evidence of the preëxisting lesion might be expected, in view of the characteristic tendency of tuberculosis to heal by fibrosis and frequently by calcification. And yet in the literature of the subject there has been scant mention of healed primary intestinal tuberculosis. Edens (7) described a radiating scar in the wall of the small intestine of a man 55 years old. The adjacent mesenteric lymph nodes were hard. Of greater significance would be the presence of calcified nodules in the intestinal wall. Such a lesion was encountered by Opie (8) in a series of autopsies performed on British soldiers during the World War. In 18 of 66 cases there was healed tuberculosis of the mesenteric lymph

nodes. In only one was there evidence of a primary lesion in the intestinal tract: a calcified, elevated nodule about 0.2 cm. in diameter was found in the mucosa of the ileum about 3 cm. from the ileocecal valve.

Because of the infrequency with which anatomical evidence of the primary entrance of the tubercle bacillus into the body by way of the intestinal tract is encountered at autopsy, and the paucity of descriptions of these lesions in medical literature, we wish to place on record several instances in which the combination of calcified mesenteric lymph nodes and a calcified nodule in the adjacent intestine was found at autopsy.

In the last 1,190 autopsies performed at the New York Hospital foci of calcification were recognized in the mesenteric lymph nodes in 33. In three of these cases a calcified nodule was found below the mucosa or elsewhere in the wall of the intestine. In an additional case, there was a small nodule of calcium in the intestinal wall but no calcium in the mesenteric lymph nodes.

REPORT OF CASES

1: Autopsy no. 7,354 (performed by Dr. Henry Brody). A 22-year-old white woman was born in England, where she lived until she came to America seven years before admission to the hospital. There was no family history of tuberculosis. She died with acute suppurative otitis media, mastoiditis, bacterial endocarditis of the mitral valve, and bronchopneumonia. In the terminal part of the ileum was a very small area of induration, on the serosal surface of which there was a small, very hard, calcified nodule. The remainder of the intestine was not remarkable in appearance. Two calcified lymph nodes were found in the mesocolon near the caecum. One measured about 1.5 cm. in length, and was composed of a gritty shell with a completely caseous centre. The other node, slightly smaller, was so extensively calcified that it could not be cut. X-ray examination of the mesentery showed large masses of calcium near its root.

Microscopic section through the lesion in the ileum showed in the submucosa, compressing and partially replacing the muscularis, an irregular mass of calcium surrounded by a zone of relatively thin fibrous tissue. There were a few lymphocytes adjacent to this, and few giant cells resembling osteoclasts or foreign-body giant cells, but no tubercles.

Microscopic section through one of the calcified mesenteric lymph nodes showed loss of lymphoid tissue. There was a dense fibrous capsule, within which was granular caseous material. Irregular granular and amorphous deposits of calcium were seen in the caseous necrosis and to a lesser extent in the fibrous tissue. No acid-fast organisms could be found.

X-rays of the lungs revealed no foci of calcification. After fixation, multiple closely placed cuts were made through the lungs, but no changes suggestive of healed or active tuberculosis were found.

2: Autopsy no. 7,897 (performed by the author). A white man, 47 years old, born in England, had lived in New York City for 21 years. One brother died at the age of 32 with pulmonary tuberculosis. The patient denied any contact with him. Death occurred with severe haemorrhage from an ulcer of the jejunum which followed a gastroenterostomy for a duodenal ulcer. In the lower part of the ileum in a fold of mucosa was a minute, firm, yellowish nodule, about 0.2 cm. in diameter. The remainder of the intestine was not unusual except for a large amount of tarry black old blood from the haemorrhage. In the mesenteric lymph nodes draining the area of the ileum in which the nodule was located, were a number of deposits of calcium. An X-ray of the mesentery showed a group of calcified foci of moderate size.

A microscopic preparation of the ileum (see figure 2C) through the nodule showed a small central mass of amorphous material, in large part stained dark blue with haematoxylin, but with outer parts stained pink by eosin. Surrounding this was a dense zone of hyalinized connective tissue containing only a few cells. There were several multinucleated giant cells with centrally placed nuclei. A zone of lymphocytes surrounded the whole nodule.

The lungs were also examined by the X-rays, and one or two very small opaque foci, 0.1 to 0.2 cm. in diameter, were seen in the upper lobe of each lung. None was found in the tracheobronchial lymph nodes. Multiple cuts were made through the lungs, and one minute gritty speck was found in the lateral aspect of the left lower lobe. No calcification was present in the hilar lymph nodes.

3: Autopsy no. 8,077 (performed by Dr. Charles T. Olcott). A white man, 29 years old, was born in New York City of Italian parents, and lived there all his life. There was no family history of tuberculosis. He died with acute bacterial endocarditis and bacteriemia (*Streptococcus haemolyticus*). In the mucosa of the ileum, about 20 cm. above the caecum, was a small, yellow, firm, very slightly elevated area, about 0.1 cm. in diameter. In the adjacent part of the mesentery was a calcified mass about 0.7 cm. in diameter. In the mesentery slightly separated from this was a larger mass composed of a number of calcified nodules.

X-ray examination of the mesentery and part of the attached ileum (see figure 1A) revealed extensive calcium deposits in the areas described in the gross, as well as a very minute speck in the small yellow nodule in the mucosa of the ileum.

X-ray examination of the lungs (see figure 1B) showed no evidence of calcification, either in the parenchyma or in the tracheobronchial lymph nodes.

Fig. 1A

Fig. 1B

Fig. 1A. Case 3. X-ray of the mesentery, showing many calcified lymph nodes. Just to the left of the solitary small calcified mass may be seen a minute deposit of calcium in the intestinal mucosa.

Fig. 1B. Case 3. X-ray of the lungs. There is no calcification visible in lungs or tracheobronchial lymph nodes.

Multiple cuts through the lungs revealed a small, soft, yellow nodule, 0.2 cm. in diameter, in the upper lateral part of the right lower lobe.

On microscopic examination the calcified mesenteric nodes showed little if any lymphoid structure. There was a dense, hyalin, outer shell of connective tissue, within which was amorphous caseous material containing considerable amounts of calcium in the form of irregular masses and varying-sized granules. There was some calcium in the hyalin capsule. No acid-fast organisms were found.

Microscopically (see figures 2A & B), in the submucosa of the ileum, compressing and partially replacing the muscularis, was a roughly irregular ring of partially hyalinized connective tissue, containing but few cells. Within this there was a space only partly filled by granular pink caseous material containing purplish calcium granules. There were seen no tubercles or giant cells. One acid-fast organism with the morphological characteristics of a tubercle bacillus was found in the caseous material of one section.

In a microscopic preparation of the lung, the small yellow nodule 0.2 cm. in diameter, was seen to consist of dense fibrous tissue surrounding a central mass of amorphous purple-staining material presumably calcium. No acid-fast bacilli were found.

4: Autopsy no. 8,173 (performed by the author). A white woman, 53 years old, was born in Hungary, but had lived in the United States for the past 35 years. She had no knowledge of diseases in infancy or childhood or of occurrence of tuberculosis in her family. She died with generalized arteriosclerosis and a large carbuncle of the back. In the mucosa of the ileum, about 250 cm. from the ileocaecal valve, and about 1 cm. from the mesenteric border, was a small, yellow, calcified nodule, about 0.1 to 0.2 cm. in diameter (see figure 3A). No calcified masses were found in the mesentery.

X-ray of the ileum containing the yellow nodule showed a small amount of calcium, but none whatever was recognized in the mesentery, and careful dissection revealed no area of caseation or calcification.

X-rays of the lungs showed two areas of calcification in the lower lobe of the right lung and one attached to the upper lobe of the left lung. Multiple sections of the lungs revealed a small area of calcification, measuring 0.4 by 0.3 cm., near the anterior inferior margin of the right lower lobe, and a slightly larger mass adjacent to the bronchus near the hilum of the right lung. Attached to the anteromedial edge of the upper lobe of the left lung by a narrow fibrous pedicle, and not actually in the pulmonary substance, was a rounded nodule about 0.5 cm. in diameter, containing a central core of calcium.

Microscopically (see figure 3B), in the submucosa of the ileum there was dense, relatively acellular fibrous tissue, forming a capsule about a space in which were many closely packed round cells with relatively small hyperchro-

Fig. 1B. Case 3. X-ray of the lungs. There is no calcification visible in lungs or tracheobronchial lymph nodes.

Fig. 2A

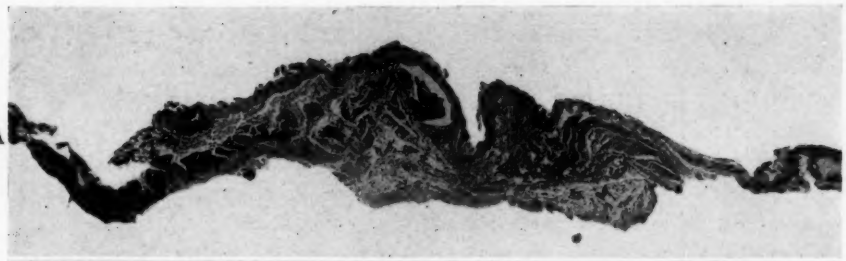

Fig. 2B

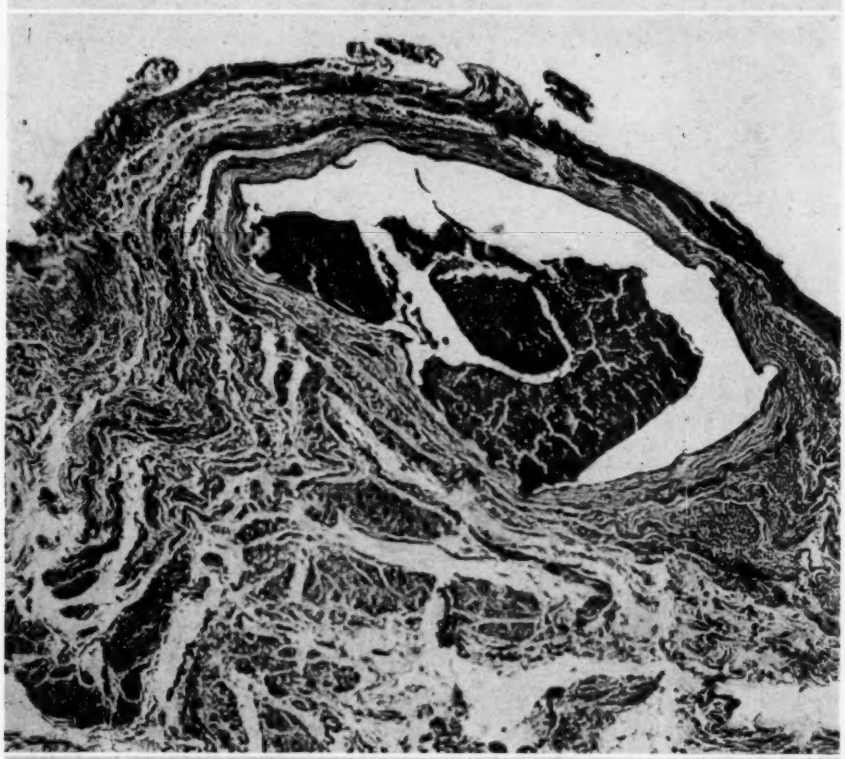

Fig. 2C

Fig. 2A. Case 3. Photomicrograph through the intestinal nodule. The irregular mass of calcium is surrounded by a fibrous capsule. × 12

Fig. 2B. Case 3. Photomicrograph with higher magnification of fig. 2A, showing caseous necrosis containing calcium, situated in the submucosa. There is surrounding fibrous tissue. The muscularis is compressed and distorted. × 86

Fig. 2C. Case 2. Photomicrograph, showing a deposit of calcium with surrounding dense fibrous tissue situated in the submucosa of the ileum. × 12

Fig. 3A

Fig. 3B

Fig. 3A. Case 4. Gross photograph showing elevation of mucosa by a nodule of calcium in the submucosa.

Fig. 3B. Case 4. Photomicrograph, showing solid masses of calcium in the fibrous capsule. Just above the calcium may be seen dense tissue resembling early bone. Above this is a multinucleated giant cell. × 210

matic nuclei. In the capsule there were some small areas of very loose connective tissue containing a few scattered cells with moderate amounts of cytoplasm and oval vesicular nuclei. In places the dense tissue was somewhat lamellated, resembling very early bone-formation, and there were irregular solid masses of calcium. Several multinucleated giant cells, with centrally located nuclei, were in contact with the calcium. A few scattered lymphocytes were present. No acid-fast organisms were seen.

Microscopic examination of the mass from the hilum of the right lung showed dense fibrous tissue with lymphocytes at the periphery. In the centre there was considerable calcium in masses and in loosely arranged granules. No acid-fast organisms were seen.

DISCUSSION

It is noteworthy that conspicuous deposits of calcium in the lungs were noted in only one instance (case 4), and in this case they were abundant. In this individual, moreover, no calcium was demonstrated in the mesentery, though there was a small amount in the wall of the ileum. If the intestinal lesion represents a healed focus of tuberculosis, there may be a reasonable doubt if it is primary and a possibility that it is secondary to the pulmonary lesion. Opie (8) has pointed out that, in those in whom the mesenteric lesions occur, focal tuberculosis of the lungs is absent or scanty. A first infection, either by way of the intestinal tract or lungs, tends to retard the spread of a second infection in the other organ.

Direct proof of the tuberculous nature of intestinal or mesenteric lymph-node lesions rests upon the demonstration of tubercle bacilli within them, either by appropriate stains, animal inoculations, or culture; or upon the presence of characteristic microscopic changes. Animal inoculations were not attempted in any instance, and in only one case (no. 3) was one acid-fast rod with the character of a tubercle bacillus seen in stained sections. It is noteworthy that acid-fast bacilli have been repeatedly demonstrated in calcified nodules of lungs and lymph nodes (9) (10) (11). The histological picture in all was suggestive of the tuberculous nature of the lesions, though not conclusive proof. There is the possibility that small areas of calcification of the intestine or mesenteric lymph nodes may be the result of infestation by parasites, as described by Wagener (3) and Beitzke (1), but there is scant probability that caseous calcified lesions are referable to this cause. With few exceptions calcified nodules of mesenteric lymph nodes are referable to

tuberculosis. Possible doubt is removed when calcified scars of the intestinal wall are associated with similar lesions of the mesentery.

Whether such a lesion may be considered as evidence of a primary intestinal route of entry of the tubercle bacillus depends on the absence of any other lesion that may be considered as primary. In the first three cases reported in this paper there was little or no evidence of a primary pulmonary lesion, since minute calcified nodules, if present (cases 2 & 3), were unaccompanied by lesions of lymph nodes. In the fourth case, as stated above, scattered calcium nodules in the lungs were accompanied by calcified foci in lymph nodes draining the areas. The evidence that is available indicates that the first three cases represent primary intestinal infection by tuberculosis. The fourth case is perhaps one of secondary intestinal infection.

It is noteworthy that, of the four cases, two of the individuals were born in England and lived there several years, a third lived her early life in Hungary, while only one was born and raised in the United States. This is consistent with the recognized higher incidence of primary intestinal tuberculosis in Europe, and especially in Great Britain.

CONCLUSIONS

1. In a small number of cases with caseous calcified or calcified lesions of mesenteric lymph nodes a healed and calcified primary lesion of tuberculosis may be found in the intestine. This lesion may be easily overlooked, and the failure to find it may be incorrectly interpreted as evidence that tubercle bacilli have passed through the intact intestinal wall to the mesenteric lymph nodes.

2. Tuberculous lesions of intestinal wall and adjacent lymph nodes are comparable to similar lesions of lungs and tracheobronchial lymph nodes (primary complex).

3. With a primary complex in the intestine and mesentery, lesions of first infection by way of the lung are likely to be absent.

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SUPERIMPOSED SPONTANEOUS PNEUMOTHORAX COMPLICATING THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

JAMES A. McCLOSKEY[3]

Collapse of a lung, with the occurrence of air in the pleural cavity, has been recognized as a clinical entity for many centuries, and it has been over two hundred years since simultaneous collapse of both lungs was first described (1).

It was not until the early years of the twentieth century that pneumothorax therapy came into common use, and it was then that the attention of phthisiologists was forcibly called to the occurrence of often the most serious and most common acute complication of collapse-therapy, spontaneous pneumothorax superimposed on artificial pneumothorax.

In order to clarify the terms and definitely limit the subject for this discussion, a review of the terminology seems apropos. The term "spontaneous" is defined (2) as "occurring without external influence;" but it seems reasonable in the present connection, and phthisiologists in general accept all instances of pneumothorax, except traumatic and induced, as "spontaneous." The limiting term "superimposed" designates that the spontaneous pneumothorax occurs on the same side as an existing therapeutic artificial pneumothorax. A superimposed spontaneous pneumothorax may be "recurrent;" and, since bilateral therapeutic pneumothorax has become an important procedure, the occurrence of bilateral superimposed spontaneous pneumothorax is a reality. If a superimposed spontaneous pneumothorax occurs on one side and the same complication occurs on the opposite side before the first side has reëxpanded there is a "simultaneous bilateral superimposed spontaneous pneumothorax." There are two such cases in our series herein reported; both recovered.

[1] From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

[2] Published by permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions drawn by the author.

[3] First Lieutenant, Medical Corps, U. S. Army.

AETIOLOGY

In the aetiology of superimposed spontaneous pneumothorax there are several contributing factors of importance. In cases in which there is tuberculous involvement of the pleura, the possibility of rupture of a tubercle into the pleural space must be considered. Therefore, it is obvious that a far-advanced case is more liable to have a spontaneous pneumothorax because of the greater incidence of pleural involvement. Unphysiological intrapleural pressure is a contributing cause of superimposed spontaneous pneumothorax; and it may be brought about by air, fluid exudate or oil in the pleural cavity. Too much air in simple pneumothorax, too much oil in oleothorax of any type, and neglected hydropneumothorax are all factors in increasing the incidence of the complication.

In cases in which there are pleuropulmonary adhesions, care must be exerted to prevent undue tension on them. There is more than the danger of a rupture of an adhesion, which is rare. The danger lies in the tearing or giving away of a necrotic area at the base of an adhesion with a resulting spontaneous pneumothorax.

Rapid changes in intrapleural pressure, such as occur during sudden paroxysms of coughing or during physical exertion, constitute an important contributing factor.

Any condition which may contribute to the formation of a superimposed spontaneous pneumothorax may be exaggerated by failure to exercise care in the technique of all phases of artificial-pneumothorax therapy.

The direct causes of superimposed spontaneous pneumothorax may be listed under six headings:

1: Rupture of a subpleural tuberculous lesion.
2: Rupture of a small pleuropulmonary adhesion.
3: Rupture of a necrotic area due to tension on an adjacent pleuropulmonary adhesion.
4: Surgical puncture of the lung.
5: Tearing of the lung substance and visceral pleura by undue pressure.
6: Spontaneous rupture of an emphysematous pulmonary bleb.

INCIDENCE

It is generally stated that 5 to 10 per cent of all fatal cases of tuberculosis have had a spontaneous pneumothorax at some time. With

the steady increase in the use of artificial pneumothorax in treating pulmonary tuberculosis, it is probable that the incidence of superimposed spontaneous pneumothorax in ultimately fatal cases is somewhat higher. However, in reviewing statistics concerning well over 2,000 patients, O'Brien and Benson (3) concluded that "spontaneous pneumothorax is much less frequently encountered since collapse therapy has become so extensively used." Of their patients, 79.5 per cent were on some form of collapse therapy.

Rubin (4) states that artificial pneumothorax is more common on the left side; therefore, the complication of secondary spontaneous pneumothorax is likewise more common on the left. Further, it is generally stated that this complication occurs in males four times as often as in females,—again partially explained by the fact that artificial pneumothorax is more common in males. But in this case there is another factor: men are more apt to exert themselves suddenly, causing rapid changes in intrapleural pressure, and this increases their incidence of spontaneous pneumothorax.

Reference to the literature reveals many conflicting ideas on the incidence of superimposed spontaneous pneumothorax, some writers expressing directly opposing opinions. For example, Pollerbeck (5) states that "Spontaneous pneumothorax is a relatively rare complication of artificial pneumothorax," while Mayer (6) is of the opinion that the occurrence of the condition "is more frequent than is generally assumed."

In briefly reviewing the literature of the last 15 years, we found that the incidence of the complication reported by different authors varies from approximately 1 to 14 per cent. Among the earliest figures were those reported by Matson, Matson and Bisaillon (7) in 1923. In 480 cases of artificial pneumothorax, they noted 16 cases of superimposed spontaneous pneumothorax, or a percentage of 3.3. Bronfin (8) reported 13.9 per cent of secondary collapse of the lung, while Swezey and Shanbar (9) noted the complication in 3.8 per cent of their cases of artificial pneumothorax. In a series of 418 cases reported from Fitzsimons General Hospital by Cooper and Stallings (10) in 1929, there were 33 diagnoses of superimposed spontaneous pneumothorax, or an incidence of 8 per cent. O'Brien and Benson had a very low incidence of the complication,—less than 1 per cent in a large series of cases reported in 1933. But they only considered cases in which there were "alarming symptoms of dyspnea, cyanosis, shock, etc." Therefore, it is not surprising that their mortality rate was excessive, being 100 per cent in

one small group of cases with far-advanced tuberculosis and 60 per cent in another.

The incidence of spontaneous pneumothorax secondary to therapeutic pneumothorax in our series of cases compares favorably with the results of others. In a series of 1,131 cases of induced pneumothorax, with 52,835 refills over a period of 6 years, the complication was noted 161 times, that is, in 14.2 per cent of the cases. It is true that the frequency of the complication seems somewhat high; but it must be remembered that at present about 64 per cent of our patients are on pneumothorax therapy, whereas in earlier years such figures were unheard of. Prior to 1931, few institutions had more than 20 per cent of patients on artificial-pneumothorax therapy, and the treatment was confined to early and moderately advanced cases. At present, approximately 50 per cent of the cases on pneumothorax in this institution are far advanced according to the *Diagnostic Standards* of the National Tuberculosis Association.

Further, the progress of pneumothorax in our patients is very closely checked by frequent fluoroscopy and in this manner many cases of asymptomatic superimposed spontaneous pneumothorax of the closed type are observed that otherwise would go undetected. All of our patients are fluoroscoped before and after all refills, and the majority of cases are fluoroscoped twice weekly, regardless of whether or not they receive air.

SIGNS AND SYMPTOMS

Superimposed spontaneous pneumothorax may occur at any time from the induction of therapeutic pneumothorax until there is complete reëxpansion of the lung. Most cases occur early in the course of treatment because the induced air acts as a foreign body, and the irritation eventually causes thickening of the pleura, both visceral and parietal, thus decreasing the liability of spontaneous collapse in later stages of the therapy.

The onset of the condition is usually sudden and often quite dramatic, although it may be rather insidious and symptomless. In the usual case, however, the patient is seized with a sharp stabbing pain on the involved side of the chest and he rapidly becomes short of breath. The pulse becomes rapid and feeble, cyanosis develops, and there is cold perspiration and an anxious expression. These signs and symptoms of shock may become less severe as the patient becomes adjusted, or, as

is more probable in the absence of immediate intervention, they may increase with a fatal termination. The signs exhibited on physical examination of the chest are not of much value in superimposed spontaneous pneumothorax because of the preëxisting artificial pneumothorax. There are however several signs of importance. The chest is fixed and often bulging on the affected side and the heart is displaced to the opposite side. Of course, there is absence of tactile fremitus, and there is tympany on percussion and absence of breath-sounds. In the asymptomatic cases the discovery of the condition is made by fluoroscopy or X-ray alone, there being no clinical signs on which to base a diagnosis.

DIAGNOSIS

The diagnosis of superimposed spontaneous pneumothorax is simple in the usual and dramatic cases, and is based on the history of therapeutic pneumothorax with a consideration of the presence or absence of any contributing or direct causes of secondary spontaneous collapse, plus the signs and symptoms exhibited by the patient.

The asymptomatic cases are diagnosed by fluoroscopy or X-ray when it is noted that the lung presents compression far in excess of that observed following the last refill; and, upon detailed questioning, the patient admits that there is a feeling of tightness in the hemithorax, and there may be a small pleural effusion. Mayer points out, however, that a roentgenogram is not always a dependable criterion of the size of the pneumothorax because no three-dimensional pictures can be obtained.

There are rare cases in which spontaneous pneumothorax presents acute abdominal symptoms that overshadow the chest symptoms (11). This is said to result from the escape of air into the mediastinum, with consequent irritation of the vagus-nerve trunks, and there are cases on record in which spontaneous pneumothorax was mistaken for an acute surgical abdomen and the patient operated upon.

In differentiating spontaneous pneumothorax from the other complications of collapse therapy, that of shifting of the mediastinum is the only one of importance and the diagnosis here is determined by X-ray.

The differential diagnosis ordinarily presents no problem, but the differentiation of the types of spontaneous pneumothorax is of value in determining the course of treatment.

In the closed type of pneumothorax the manometer reading reaches a

certain positive and becomes constant, showing that no more air is entering the pleural space. However, if the fluctuation is constant from a certain positive to a certain negative, even after air has been withdrawn, the pneumothorax is of the open type. If, on the other hand, there is a constantly increasing positive pressure, as shown by the manometer readings, the pneumothorax must be of the valvular type. In each case the symptoms and signs will be parallel and in proportion to the type and extent of pulmonary collapse as indicated by manometric readings.

TREATMENT

The accident of a spontaneous pneumothorax during the course of artificial-pneumothorax therapy may require no special treatment, or it may require immediate measures to prevent a fatal termination. If the pulmonary compression resulting from the increase of air in the pneumothorax space is sufficient to close the pulmonary fistula and the patient is not yet unduly dyspnoeic, nothing need be done. However, if the patient shows signs of cardiorespiratory embarrassment, air should be removed by the pneumothorax apparatus. This makes the patient more comfortable, and the reduction of the intrapleural pressure may prevent the formation of a pleural effusion. Pulmonary compression should not be reduced to such an extent that the fistula may again become patent.

In the case of the silent or relatively closed type of superimposed spontaneous pneumothorax in which no immediate treatment is necessary, the question of reëxpansion of the lung to an optimum degree of compression is important. If the patient is neglected a further complication may arise. Without careful regulation a high negative intrapleural pressure will develop, with a resulting severe pleural effusion, which, if neglected, may become purulent. Therefore, the patient should be put on a regimen of repeated fluoroscopy, and occasional manometric readings taken to prevent the formation of a high negative intrapleural pressure. In this manner the lung is very slowly and gradually brought back to its optimum degree of compression, and simultaneously any effusion that occurred will usually disappear.

If the pleuropulmonary fistula is large and remains patent or is of the valvular type, it is necessary to introduce a retention needle connected to a water-valve. This allows the removal of air from the pleural space, reduces the intrapleural pressure, and allows the continuous

escape of air during coughing, expiration, etc. The retention needle should be retained in place, with the water-valve attached as long as there is sufficient intrapleural pressure to cause an escape of air-bubbles through the water. In order to lessen the chances of infection, however, it should be removed as soon as possible. As a retention needle we use a standard 2-in., 15-gauge needle, with a Pollock needle-retainer or a Swift needle-holder attached. This allows the needle to be inserted to the correct depth and to be securely strapped in place.

Strict asepsis in the aspiration of air and insertion of retention needles is imperative if the complication of pyopneumothorax is to be kept at a minimum.

Supportive and symptomatic treatment consists in the use of codein to relieve pain, cough and apprehension, and oxygen to combat the cyanosis and dyspnoea. We do not use morphine or other strong narcotics, such as dilaudid or pantopon, because of the excessive depression that may hide important symptoms.

If congestive heart failure threatens, digitalis is indicated, digitalization by the rapid method usually being imperative. Bruns (12) states that, if the right heart becomes embarrassed and the uncompressed lung congested, venesection is indicated. We have never resorted to this procedure. As a further support for the heart, glucose in the form of syrup, should be given. About six ounces of Karo syrup daily is sufficient, but many patients cannot tolerate such a dose orally; so intravenous glucose may have to be given if there is any question concerning the glycogen supply in the event of a failing myocardium.

These patients, being in shock, are treated accordingly, with one notable exception. They are kept warm by the use of blankets and hot-water bags and are given stimulants when indicated, etc.; but, instead of the shock or Trendelenburg position, the semierect or Fowler's position is used in order to relieve the orthopnoea as much as possible.

COMPLICATIONS AND SEQUELAE

Superimposed spontaneous pneumothorax may be a serious complication of collapse therapy; but this condition has further complications that, when they occur, seriously threaten the success of collapse therapy and often are a serious menace to the patient's life.

The exercise of proper care in the technique of artificial pneumothorax, along with due recognition and careful avoidance of the contributing and direct causes of superimposed spontaneous pneumothorax, will go

far in the prevention of the condition and its complications; but there are occasions when the utmost care will be unavailing.

If the patient survives the spontaneous collapse of the lung with its attendant shock he may have an uneventful recovery, or his survival may be challenged by one or more of the following complications:

1: Congestive heart failure may occur, due to the unbalanced mechanics of thoracic circulation caused by the spontaneous pneumothorax.

2: Pleural effusion, the most common sequel of the condition, may be simple and transient, or it may be massive and require repeated aspirations.

3: Empyema is one of the most serious of the complications and it may be of the pure tuberculous type or the mixed-infection type (13). In either case the condition must be treated intensively if the patient is to survive. In our series of 161 cases of superimposed spontaneous pneumothorax, empyema occurred 26 times, the incidence being 16.1 per cent. Of these cases, 6, or 23 per cent, died while still patients on the Tuberculosis Service. The actual mortality rate was much higher, however, because several died after transfer to the Surgical Service for thoracoplasty or unroofing of the empyema pocket.

The incidence of empyema increased in direct proportion to the length of time the retention needle was necessary, but two cases were notable in that the retention needle was in place for ten and fourteen days, respectively, with no subsequent development of pleural effusion of clinical significance. These cases serve to emphasize the importance of careful aseptic technique in the insertion of retention needles.

4: A patent bronchopleural fistula results in a persistence of the lung collapse. It also results in a serous exudation which soon becomes infected from the bronchial tree with a resulting pyopneumothorax, if the patient survives. The fistula may be closed by proper treatment of the spontaneous pneumothorax or during treatment of the empyema; or, as a last resort, thoracoplasty may close it, but this also fails in some cases.

5: Surgical emphysema occurs to some degree in almost all cases in which a retention-needle is used, but careful strapping of the needle in place, so that it is snug and as firm as possible, prevents this complication from becoming serious in the majority of cases. Two of our recently fatal cases had a very extensive generalized emphysema in spite of all possible precautions.

6: Obliteration of the pneumothorax, complicating spontaneous pneumothorax, is the result of an acute pleuritis caused by the irritation of the pleura.

7: Mediastinal displacement may occur, and is due to the positive pressure in the hemithorax pushing the mobile mediastinum to the opposite side. This does not occur in patients who have had artificial pneumothorax for some time, because the mediastinum has become firm and relatively immobile.

8: Mediastinal hernia of the lung results from the same causes as mediastinal

displacement, and in each case proper treatment of the spontaneous collapse of the lung relieves the complication as well.

9: Other rare complications are pneumopericardium, pneumoperitoneum and contralateral spontaneous pneumothorax.

PROGNOSIS

In general, the immediate prognosis of superimposed spontaneous pneumothorax is fairly good; but there is always the danger of a recurrence of the condition, which occurs in about 25 per cent of the cases. Since it occurs most commonly in far-advanced cases the ultimate prognosis is poor.

The mortality rate of spontaneous pneumothorax during the course of artificial pneumothorax, as given by various authorities, ranges from 25 to 100 per cent.

In our series there were 26 deaths, a mortality rate of 16.1 per cent. This is lower than that reported by most phthisiologists for the same reason that our incidence is somewhat higher, that is, because of the diagnosis, made by repeated fluoroscopy, of many asymptomatic cases.

SUMMARY

1. Superimposed spontaneous pneumothorax is often a most serious and also the most common acute complication of artificial-pneumothorax therapy in pulmonary tuberculosis.

2. The condition has several contributing and direct causes which, by the exercise of diligent care, can be reduced to a minimum, but some cases are unavoidable.

3. In a series of 1,131 cases of induced pneumothorax with 52,835 refills, secondary spontaneous pneumothorax occurred 161 times, an incidence of 14.2 per cent.

4. There are several complications of superimposed spontaneous pneumothorax, the most important being empyema, surgical emphysema, patent bronchopleural fistula, mediastinal displacement, mediastinal hernia of the lung, and congestive heart failure.

5. In our series of 161 cases there were 26 deaths, a mortality rate of 16.1 per cent.

6. The mortality rate of superimposed spontaneous pneumothorax in relation to the total number of induced pneumothoraces was 2.3 per cent.

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THE ISOLATION OF PATHOGENIC BACTERIA FROM THE AIR

A Dissertation in Bacteriology[1]

RALPH PRESSMAN

1. PATHOGENS EXCLUSIVE OF TUBERCLE BACILLI

Although many findings have been presented showing the possibilities of aerial transmission of pathogenic organisms, the problem is still in dispute.

Whipple (36), in 1915, reviewing and summarizing the work on aerial transmission states:

> Some very thorough and conclusive work has been presented in recent years to show that the danger of infection by pathogenic bacteria carried through the air for any considerable distance is very slight in the majority of places occupied by human beings. The work of Chapin on droplet infection and of Winslow in the schools of New York City are notable in this field, and have been generally accepted as representing the true condition.

Chapin (7), although accepting the theory of aerial transmission, states that diseases are not easily transmissible.

On the other hand, Huddleson and Hull (16) report that 16 per cent of the organisms found on blood plates exposed to the air of an amusement hall, eight days after the outbreak of an epidemic of colds and coughs, were streptococci showing the alpha type of haemolysis.

Many different methods have been devised for studying the bacterial content of the air. Referring to the methods of sampling Weinzirl and Fos (33) state, "So numerous are the schemes that practically no two investigators use the same one, and as a result it is quite impossible to estimate the accuracy and value of the data thus far obtained." They further state, "The devices used up to 1910 may be summarized and divided into three general methods, viz. (a) precipitation of bacteria by gravity, (b) bubbling air through some liquid, and (c) filtering air through some granular solid."

[1] Presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1936.

In 1916, the Committee on Standard Methods for the Examination of Air (1), in an attempt to arrive at some uniform method of air sampling, recommended the Sand Aeroscope for collecting bacteria from air.

McConnell and Thomas (22), in 1925, made a study of the several different methods employed in collecting air, comparing the results with those obtained using the standard method. They point out several disadvantages inherent in the standard method and suggest a modified water aeroscope.

Wells (34), in 1933, described an instrument, the Wells Centrifuge, which he developed for the sampling of air. Later, in 1934, making use of this apparatus, Wells and Stone (35) were able to isolate experimentally, among others, such organisms as *Diplococcus pneumoniae type I*, *Corynebacterium diphtheriae*, *Streptococcus haemolyticus* and *Streptococcus viridans*. These organisms, representative of the flora of the respiratory tract, were recovered two days after dilutions of the organisms had been atomized into an experimental tank. If such results could be obtained under practical conditions, the bacteriology of the air would take on a new significance. Indeed, proof that such organisms could remain alive and suspended in the air for two days, even under the controlled conditions practised by Wells and Stone, reopens the question of aerial contamination.

In view of the inconsistencies in results with other methods, Wells's apparatus, which promised to overcome some of the existing errors, seemed of interest.

The work described here was undertaken in an attempt to (1) evaluate the Wells centrifuge under practical conditions; (2) to compare results with the Wells centrifuge with the results obtained, using the classical petri-dish method; (3) to cover a field wide enough to be compatible with some definite conclusions; and (4) to test the efficiency of an air-conditioning apparatus, for which the Wells centrifuge seems to be aptly suited.

Apparatus

The Wells centrifuge (34) is described briefly by Wells as follows:

> The rapid revolution of a glass cylinder about its vertical axis causes a current of air to enter through a central axial tube and to escape along a thin layer of nutrient medium supported on the walls of the cylinder. Particles suspended in the air are deposited on the medium. Colonies develop where the

individual bacteria have been precipitated and can be counted with the naked eye.

The complete procedure of making a test is described by Carpenter (6) as follows:

A thermos bottle used for carrying melted agar into the field, is sterilized for 30 minutes at 15 pounds pressure. Nutrient agar heated at the same pressure and time is poured into the thermos bottle. The sterile defibrinated blood is aseptically transferred into the small dropping vials that have been heated for an hour at 170°C. The special centrifuge tubes are sterilized for 30 minutes at 15 pounds pressure, preferably a day or two in advance so that any moisture that may have accumulated will have a chance to evaporate. When the operator is ready to make a test, a manometer is connected to the intake pipe by means of a calibrated nozzle. The machine is started and the manometer is adjusted. The machine is then stopped and the nozzle is removed so that the intake pipe may be swabbed with alcohol. After this the nozzle which has also been swabbed and plugged with cotton is again inserted. A special centrifuge tube calibrated to hold 20 cc. is then filled to the mark with agar and 0.6 cc. of blood from a graduated dropper is added. The tube is then rotated gently to mix thoroughly so that there will be no areas of agar lacking blood. The tube is inserted in the centrifuge head and the machine is started immediately. As soon as the water level in the manometer has risen to its maximum height, a record of the time is kept by means of a stop-watch.

A table giving the corresponding number of cubic feet of air for manometer readings ranging by tenths from 0.1 to 3.0 inches accompanies the machine. Carpenter (6) found that the average manometer reading with Philadelphia current was 1.3 inches or 1.36 cubic feet of air per minute. All tests were of 10-minute duration averaging 13 cubic feet of air, which seemed to be a representative sample. After the ten-minute interval the machine was stopped and the tube removed. A rubber stopper, covered with tin-foil, was inserted in the tube. The tin-foil was removed before incubation at 37° C. for 48 hours, after which the tubes were marked off and the colonies counted. By means of a special loop several colonies, usually eight, were fished from the tube, inoculated first into a tube of 5 per cent blood-infusion broth, then streaked on 5 per cent whole-blood agar plates, and where possible a direct smear was made. The blood-infusion broth was made with double-strength beef infusion containing Parke-Davis peptone. Five

per cent whole blood-agar plates were made as follows: To 500 gm. of veal was added 5 gm. salt, 10 gm. peptone and 20 gm. of agar per litre of medium. The pH was adjusted to 7.4. Defibrinated horse blood was added to amounts sufficient to make 5 per cent blood agar. For the identification of ordinary air-borne organisms the usual laboratory media were employed. The organisms were classified according to Bergey's *Manual* (4).

Choice of Location

A series of scarlet-fever outbreaks among children in Philadelphia suggested school-rooms as sites suitable for some of these experiments. Through the coöperation of Dr. Cornell, Medical Director of Public Schools, schools where recent outbreaks had occurred were selected. As controls, schools in the same neighborhood, but free from cases of scarlet fever, were selected.

Records of the weather conditions, temperature of the room, the prevailing ventilating system, number of pupils occupying each room, the exposure, the doors and windows present, and other data pertinent to the results and interpretations, were made at the time of sampling. These variable conditions did not affect the results.

Method

The Wells centrifuge was usually placed in the front part of the room, while the class was in session, approximately at the children's sitting level and from three to five feet from the front row. No attempt was made to alter the routine of the class-work. The teacher was encouraged to proceed as normally as was possible in the presence of a distracting motor in operation. A blood-agar plate was exposed simultaneously with the starting of the centrifuge. The plate was placed at the same level of the centrifuge and about a foot away.

From one to two hours elapsed between the time of collection and the incubation of the exposed media. The incubation was carried out at 37° C. for 24 and 48 hours.

Other Sites for Air Sampling

In addition to 80 classrooms (average size being 30 x 20 x 12 feet and holding between 40 and 50 pupils), the air of four tuberculosis sanitoria, described later, as well as that from a large lecture room in each of two colleges, seating 120 and 80 students respectively, was sampled.

The results indicate that, though quantitatively there were more organisms present in the Wells tube than on the blood-agar plate, qualitatively there was no difference. The organisms most frequently met were members of the *B. subtilis* group (*B. mesentericus, B. mycoides, B. subtilis*); members of the *Micrococcus* genus (*M. flavus, M. aurantiacus*); members of the *Sarcina* genus (*S. flava, S. subflava*); members of the *Staphylococcus* genus (*S. epidermidis, S. aureus, S. citreus*); actinomyces; yeasts and molds, identification of which was not attempted.

Use of the Wells Centrifuge to Determine the Effect of an Ozonizer on the Bacterial Content of a Room

The air in a large amphitheatre accommodating 120 students was tested after having been occupied from 9 A.M. to 11 A.M. Ten minutes after dismissal of the last class the air was sampled. An ozonizer was then operated for a period of 15 minutes, at the end of which time the odor of ozone could be detected at the far end of the amphitheatre. The Wells centrifuge was run for two 10-minute periods after the ozonizer was turned off, thus obtaining two different samples of air. These tests were repeated a week apart. The results indicate that there was no appreciable decrease in the number of organisms after 15 minutes of ozonization even though the Wells centrifuge was placed three feet from the ozonizer. Qualitative observations were not made in these experiments since the quantitative findings did not seem to warrant such additional work.

DISCUSSION

Though in principle the Wells centrifuge seems well adapted to the sampling of air, in practice the author met with a serious difficulty in that the water of condensation on the inside of the Wells special tube interfered with cultural isolation upon which depended subsequent identification. The liquified medium, cooled to about 45°C., was poured into the Wells tubes. Since these experiments were carried out in winter, and the time between sampling and incubation ranged from one to two hours, droplets of moisture were formed as a result of sudden temperature change when the tubes were placed in the incubator. These droplets on rolling down the walls of the tube produced mixed colonies which necessitated separation before identification was possible, a procedure both tedious and misleading, since the spore-formers outgrow the other organisms. Several attempts were made to overcome

this difficulty. The method which was finally found best was that of drawing out a test-tube, 6 x $\frac{5}{8}$ inches, filing through the constricted part, and filling each end with cotton, then glass wool, and in the centre calcium chloride was placed. This tube was forced through the opening in the rubber stopper and extended two inches into the tube. Sterility had to be maintained, and, though this device and procedure proved satisfactory, it was found to be troublesome and not practicable. Wells and Stone, it seems, in carrying out their experiments, sampled the air in the same building in which the tubes were to be incubated, thus avoiding this difficulty.

A heavily polluted environment, due to the stirring up of dust as in the movement of children in the class-room or an unusual air current, had a tendency to introduce numbers of organisms producing either colonies too numerous to count and isolate, or spreaders which covered the entire field. This difficulty, which gives end-results that are valueless, cannot be controlled. In the classic experiments of Wells and Stone, working with pure strains, the difficulty of crowding, when met, was controlled by dilution. The number of colonies in any given tube may be controlled by the length of time of the aspirating period. However, the bacterial content of a room is unknown, and it did not seem wise to vary the time of aspiration and thereby add another variable. A variation in time, unless proved experimentally otherwise, appears not to be compatible with comparable results.

In some cases a large percentage of the organisms was precipitated on the lower portion of the tube. Under these conditions, it was impracticable and at times impossible to remove colonies in a pure state from this portion of the tube.

In view of these difficulties, whatever else might be said in favor of the Wells centrifuge, the fact remains that, in so far as practicability is concerned, its value will be limited unless changes will find it more effective.

One hundred samples of air collected by the Wells centrifuge revealed the presence of no bacteria other than those commonly considered airborne and generally not held responsible for infection.

Chapin (7) feels that, "There may be pathogenic organisms actually present in the air, yet they may not be dangerous, either because they have wholly or partially lost their virulence, or because they are too few in number, or for some other unknown reason."

Winslow and Robinson (37), in an investigation of the pollution of the atmosphere by mouth-spray, state that, although cultures inoculated

into the mouth are discharged in large numbers in the act of speaking and are found as far as 7.5 metres from the person, actual mouth inhabitants, streptococci for example, could not be demonstrated in large numbers even at 15 cm. from the mouth of the speaker. The examination of 74 litres of air exposed to mouth spray by vigorous speaking, at a distance of 35 cm. to 2.4 metres, showed no streptococci.

Koeniger, quoted by Winslow (37), reported that 60 per cent of the bacteria in the mouth-spray disappeared from the air in ten minutes and that in twenty minutes less than 10 per cent of the original number remained.

Thompson (32) reports that of 3,377 cases treated in the ward, cross-infection with scarlet fever occurred only nine times, measles thirteen, chicken-pox twenty, whooping cough six, and mumps once. Teague (31) found that, in diphtheria, patients frequently emit the organisms while talking and coughing, but in small numbers only.

Rosenau (27) maintains that, the more transmission of communicable disease is studied, the less is air implicated.

In view of the difficulties enumerated when using the Wells centrifuge, definite conclusions concerning the possibility of aerial pathogens cannot be drawn. The results, using the blood-plate method, however, agree with those of most workers.

SUMMARY

1. One hundred rooms, distributed among twenty public schools, four tuberculosis sanitoria and two colleges, were sampled using both the Wells centrifuge and the blood-plate method. Under practical conditions the centrifuge presents many difficulties.

2. The two methods used gave similar qualitative results.

3. The results of the experiments seem to indicate that the possibility of isolating pathogens under the above conditions is slight.

4. It was shown that an ozonizer did not reduce the number of organisms present in a given environment.

2. MYCOBACTERIUM TUBERCULOSIS FROM AIR AND DUST

The mode of transmission of tuberculosis has been studied extensively. Due to the many conflicting results reported, it is not surprising that it should have become the subject of much controversy. Neufeld (23), discussing the origin of tuberculosis, enumerates thus the points around

which so much confusion has grown: "The question whether tuberculosis as a rule is transmitted by the bacilli entering by way of the lungs or by way of the pharynx and the nose; whether moist droplets or dry dust constitute the chief agent; whether the entrance of large numbers of bacilli have severer consequences than that of few bacilli; or whether the germ of human tuberculosis is identical with that of the bovine disease, etc." are controversial ones by their very nature and will probably never satisfactorily be answered.

The results obtained by earlier workers form the basis upon which some of the existing views are founded. Cornet (10), for example, supporting Koch's opinion that contagion is conveyed mainly by dust, inoculated guinea pigs intraperitoneally with dust collected from rooms occupied by consumptives. He demonstrated virulent tuberculosis in 15 of 27 samples of dust from seven hospitals, 3 of 9 samples from insane asylums, 21 of 43 samples from the homes of six patients.

Hill (14), following Cornet's methods, obtained virulent bacilli in but 5 of 496 swabbings from private houses where there were cases of disease, and in 3 of 180 swabbings from hospital wards.

Heymann (13) found virulent bacilli in 44 out of 239 specimens of dust from rooms of tuberculosis patients in hospitals, and in private homes 14 of 116 samples.

Coats (8), following Heymann's methods, was able by inoculation tests to demonstrate the presence of tubercle bacilli in 66 per cent of specimens of dust obtained from 14 rooms occupied by tuberculous patients.

Contrary to these findings, Kirstein (17) experimenting with various kinds of dust could not find living tubercle bacilli after 8 days.

Cadeac (5) was unable to reduce sputum to dust until it had been dried ten to twelve days, while the tubercle bacilli had been nearly vitiated on the sixth day.

Sticher (29) and Beninde (3) found it difficult to demonstrate living bacilli in dried and pulverized sputum under natural conditions.

Augustine (2), making use of a suction-pump, met with little success in demonstrating tubercle bacilli in a tuberculous environment.

The divergences in results are due in part, at least, to the varying methods employed in obtaining samples of dust for examination. Indeed, the lack of uniformity in results may bear a direct relationship to the methods used in the collection of the sample.

Of all the phases in the study of tuberculosis, that of collection of

material has received the least attention. The methods for collection and examination of air and dust, which are discussed in part 1 of this paper, have been crude and varied.

In the literature some statements appear so regularly that one may consider them as basic truths:

1: That tubercle bacilli, if present, in the air and dust are to be found only in small quantities.
2: That, if found, depending on the length of time of exposure, they have lost some or all of their virulence and viability.
3: That tubercle bacilli may live from 6 to 10 days after the sputum in which they were found has been dried and disappeared as dust.

Any new method of collection that is to be devised must, therefore, take into consideration the above factors, must reduce the number of variables to a minimum or even to a constant.

This work was undertaken for the purpose of (1) determining the efficiency of the Wells centrifuge in collecting air for the isolation and identification of tubercle bacilli in a tuberculous environment; (2) to attempt to devise a simple standard method for the collection of dust for the isolation and identification of tubercle bacilli; (3) to determine the relative efficiency of the several media for culturing tubercle bacilli from air and dust; and (4) to determine the relative efficiency of oxalic acid as a digestant when the suspected material is present in an aqueous suspension of dust.

Selection of Digestant

Petroff (26), in 1916, succeeded in isolating tubercle bacilli from sputum and other materials in which other species were present. His technique, which made use of a 3 per cent solution of sodium hydroxide, did much to stimulate the use of cultural methods. In 1924 Loewenstein (21) suggested the use of acids as digestants. Previous to this time antiformin was presented and employed as a digestant with favorable results. Corper and Uyei (11) in 1926 made a comparative study of digestants, and concluded that oxalic acid in a concentration of 5 per cent was most efficient.

Though a 5 per cent solution of oxalic acid was found to be well suited for sputum, the fact that (1) fewer organisms were to be expected in an aqueous suspension of dust; (2) that in all probability, if organisms were present, some would have lost their viability; and (3) that the

purulent material surrounding the organisms, as is the case in sputum, would not have to be penetrated, strongly suggested that a 5 per cent solution of oxalic acid might be so strong as to further vitiate the relatively few organisms that may originally have been present. It was, therefore, deemed advisable to try four concentrations of oxalic acid, namely, 0, 1, 3 and 5 per cent.

Selection of Culture Media

With the development of suitable digestants a number of promising culture media have gained favor. Indeed, the use of culture media for the growth, isolation and identification of tubercle bacilli has been suggested as a substitute for the classical guinea-pig method. Thus, Holmes (15), after a comprehensive study with tuberculous material employing Jensen's medium, says, "The use of this medium makes the use of guinea pigs all but superfluous. On this medium rich growth resulted in five or six days." In the same vein, Norton (24), among others, attests to the economy of culturing the organisms as against the animal-inoculation test; also, a positive culture is known to have more absolute value than a positive inoculation result, for guinea pigs have been known to contract tuberculosis spontaneously.

On the other hand, Stadnichenko and Sweany (28) claim that animal inoculation is still the method of choice in diagnoses under some conditions, and with them also Feldman and Magath (12) attest to the reliability of inoculation of guinea pigs as a means of designating the tuberculous nature of clinical material of an obscure character. The most serious objection is the time before a diagnosis can be made. Animals should be killed eight weeks after injection.

While the results with artificial culture media seem very encouraging, in this work, however, in which relatively small numbers of tubercle bacilli were expected, guinea-pig inoculations were also made.

The author has, on several occasions, made use of Corper and Uyei's crystal-violet-glycerin-water-potato medium (11) and Petroff's gentian-violet-egg medium (26). Both of these served very well, Corper and Uyei's medium being somewhat more efficient. In the work to be described, use was made of the above media, as well as that of Petragagni's milk-peptone-potato-egg-glycerin medium (25) and Sweaney-Evanoff medium containing veal-egg-cream-milk (30), which, from recent reports, seemed to be highly regarded.

Selection of Institutions

Since an attempt was being made to appraise methods of collection, it seemed obvious that every type of situation should be considered in evaluating the results of such work. With this in mind four institutions were selected in different localities, and varying in construction, management and personnel. Of the four, three are in Pennsylvania, one in New Jersey, two in a suburban area, and two in a metropolitan area. Two extremes were selected, one the last word in modern hospitalization; the other lacking in much that is considered essential. Between these extremes were two intermediate institutions, well endowed and supervised, both in a metropolitan area. The four sanitoria were selected as being representative of all possible conditions.

The coöperation of the staffs in all cases was most satisfactory and the author hereby wishes to express his thanks. For obvious reasons the names of the institutions are omitted.

Institution A: This sanatorium is situated in Pennsylvania in the open country about 20 miles from a large city. It is set well back from the main road and is well isolated from traffic dust and noises. The building itself is so constructed as to embody the most modern principles of hospitalization. The fact that the majority of patients occupy private rooms makes this institution unique as compared to the other hospitals visited.

Institution B: This hospital, which is well supervised, is also located in Pennsylvania in a metropolitan area where there is a moderate amount of traffic. The building, which is of modern construction, is well kept. Every week, the walls and floors of all the rooms and corridors are washed with soap and water to which has been added a cresol solution.

Institution C: This is a well supervised hospital in Pennsylvania situated in a metropolitan area and in the heart of traffic. The neighborhood is populated by members of the middle and poorer classes. The building is of comparatively modern construction and is kept reasonably clean. The majority of the patients are Negroes who come periodically to the hospital for observation and treatment.

Institution D: This hospital is located in New Jersey about 15 miles from a large city. Although it is situated in the open country, the grounds proper are not well kept. Four wooden bungalows, which

house the patients, comprise the sanatorium. The hygienic conditions in general are very poor. Aside from the fact that there is an abundant supply of air, the rooms, in which a large amount of dust had accumulated, were dirty. The institution is very poorly endowed, the results of which were very apparent.

Included in these four institutions, wards accommodating up to eight patients as well as private rooms were sampled. In each institution the pneumothorax room and the fluoroscopic room were sampled.

Methods

Apparatus: A number of porcelain evaporating dishes, 50-cc. capacity, with outside diameter of 10 cm., free from scratches were carefully cleaned, placed in a metal box and sterilized in a hot-air oven. The box was kept tightly closed, and in it the sterilized dishes could be kept indefinitely before use.

The Wells centrifuge, described above, was used.

Collection of material: Into each of four evaporating dishes 20 cc. of normal saline solution were added. The dishes were numbered, and a dish was placed on the floor in each corner of the room where it was exposed for one week. The water lost by evaporation during exposure was not restored. The accumulated dust residue was taken up with 2 to 3-cc. portions of sterile saline solution, transferred to a sterile graduated centrifuge tube, the volume was made up to 10 cc., and the tubes were taken to the laboratory.

The Wells centrifuge, described in part 1 of this paper, was used. To the special Wells tube 20 cc. of sterile saline solution was added. The machine was placed in the centre of the room and allowed to aspirate air for twenty minutes, during which time about 27 cubic feet were aspirated. The contents of the tube were transferred to four sterile graduated centrifuge tubes. The Wells tube was rinsed with sterile saline solution, and the rinsings were added to the centrifuge tubes so that the final volume was 10 cc. The tubes were then taken to the laboratory.

Treatment of material: At the laboratory the numbered tubes were centrifugated at high speed for 10 minutes. The supernatant fluid was poured off, after which a smear of the residue was made on a slide previously prepared with Mayer's albumin fixative.

Digestion of the residue: After making the smear, the remaining residue

was stirred, water added to the 1-cc. mark, and an equal volume of the appropriate concentration of oxalic acid was added. The tube was shaken, after which it was placed in the incubator at 37° C. for 30 minutes, the tube being shaken several times during the period of incubation. In order to free the mixture from oxalic acid the tube was centrifugated for 10 minutes, and the clear supernatant fluid was discarded. To the residue, distilled water was added and the tube again centrifugated. The process of washing was repeated three times, after which time the residue was neutral to litmus. After the final washing, the supernatant fluid was decanted and the residue, from which another smear was made, was ready to be transplanted on the several media. The relative efficiency of the various concentrations of oxalic acid is shown in table 1.

TABLE 1

Showing the relative efficiency of various concentrations of oxalic acid in reducing contamination by yeasts and molds

CONCENTRATION OF OXALIC ACID	TOTAL NUMBER OF CULTURES TREATED	NUMBER OF CULTURES CONTAMINATED	PERCENTAGE OF CONTAMINATIONS
per cent			
0	54	24	44
1	56	29	51
3	60	20	33
5	60	15	25

Inoculation of media: (a) *Primary cultures:* The digested and washed residue was used to inoculate the several culture media. A standard platinum loop, 4 mm., 23 gauge, was used for the transfer. Before incubation the cotton plugs were immersed in a vaseline-paraffin mixture. Incubation was at 37° C.

(b) *Secondary cultures:* Macroscopic examination of the primary cultures were made periodically. The tubes showing gross contamination at the end of two weeks were discarded. Forty-nine days after incubation the uncontaminated tubes were examined. Macroscopically, the colonies were small and rather atypical. Subcultures on 3 per cent glycerol-agar and smears of the growth were made.

Staining technique: That used throughout this work for the staining of direct smears was Ziehl-Neelsen's, as modified by Cooper (9). The results of the stained preparations before and after digestion, as well as the results of the primary and secondary cultures are given in the

composite table 2. The technique used for tissue sections was that of Klingmuller (18).

TABLE 2

Results of smears and cultures for tubercle bacilli

	INSTITUTION				TOTAL
	A	B	C	D	
Number of rooms examined	3	4	4	4	15
Number of samples collected	11	15	16	13	55
Per cent of smears positive before digestion	100	66	89	100	89
Per cent of smears positive after digestion	90	66	93	92	86
Total number of primary cultures	44	58	64	64	230
Per cent contaminated after two weeks	23	34	39	55	31
Number of primary cultures uncontaminated	34	38	39	29	140
Per cent of positive primary cultures for tubercle bacilli	44	63	67	14	49
Number of secondary cultures made	15	24	26	4	69
Per cent of positive secondary cultures	13	67	24	75	45

Experiments on guinea pigs: (a) *Primary inoculations:* The remaining residue of each sample, after the slides and cultures were made, was stirred in the centrifuge tube with a small quantity of sterile saline solution, thoroughly agitated, and the suspension filtered through several layers of sterile gauze. A composite of all the washings of one room was used to inoculate the guinea pigs. One and one-half cubic centimetres of the mixed, filtered washings, again agitated, was injected intraperitoneally into each of two guinea pigs. (Stained preparations of the washings showed many acid-alcohol-fast organisms.) The guinea pigs were weighed periodically. Their weight and behavior were apparently normal.

Groups of animals were killed 72, 90, and 120 days after inoculation. The animals were chloroformed and the abdomen opened under aseptic conditions. The organs were carefully examined and cultured; smears, and sections of the spleen, lungs, and liver were made and stained. The results of the stained smears and sections were all positive.

(b) *Secondary inoculations:* The secondary cultures were positive after three weeks' incubation. The tubes showing microscopic evidence of tubercle bacilli were grouped according to institution and the growth in the tubes corresponding to a given institution was washed down with

sterile saline solution and pooled. The final concentrated bacterial suspension was then diluted to a volume of 5 cc. Guinea pigs were inoculated intraperitoneally with 4 cc. of this suspension.

This group of animals was killed 72 days after inoculation, and all lungs were tuberculous. Glycerol-agar cultures made from the lungs were positive after three weeks' incubation. Sections made of the lungs were also positive.

DISCUSSION OF RESULTS

The striking fact arising from this work is the overwhelming number of positive results obtained on direct smears, culturally and on guinea-pig inoculations. Indeed, the ease with which the organisms were isolated suggest that much had been overlooked by some earlier investigators. The fact remains that, by the simple expedient of exposing four dishes containing saline solution in the corners of a room for one week, tubercle bacilli, if present, can be isolated and identified by bacteriological technique.

In the composite table 2, it will be seen that of 55 samples tested by the dish method 48, or 87 per cent, were positive. On the other hand, in using the Wells centrifuge the findings were all negative. It should be noted that this is not a reflection on the apparatus, but rather emphasizes, in agreement with others (10)(19), that the number of organisms present in the air of even a tuberculous environment is relatively small.

Referring to the concentration of tubercle bacilli in the air, Cornet (10) considers that Mycobacteria are so sparsely distributed that one ought not to expect them by filtration of even 1000 litres of air. This may, in a sense, explain why some workers have failed to find the organisms in tuberculous environments.

Since the result is a function of the concentration of dust collected and the volume of material used in the cultures, smears and guinea-pig inoculation, the few negative findings lose their significance.

There is no question that the method of digestion herein used can be improved upon; for example, the 5 per cent oxalic acid used as a digestant falls short of being completely efficient. Since contamination of the cultures is a function of the environmental cleanliness in which a sample is obtained, as shown in table 3, a digestant might be developed which would be efficient against the greatest degree of contamination.

TABLE 3

Showing that the cleanliness of an environment has a distinct influence on the contamination of cultures

INSTITUTION	NUMBER OF ROOMS	TOTAL CULTURES	NUMBER CONTAMINATED	PER CENT CONTAMINATED
A	3	44	10	23
B	4	58	20	34
C	4	64	25	39
D	4	64	35	55

It is significant, too, to point out the rôle of the dyes in the culture media. From table 4 it will be seen that the media inhibiting growth of contaminants are, in the order of their efficiency, Petroff's, Petragagni's and Corper's. All three of these served almost equally well.

TABLE 4

Showing the effect of incorporating a coal-tar dye in a medium upon yeasts and molds as contaminants

CULTURE MEDIUM	TOTAL CULTURES	NUMBER OF CONTAMINATED CULTURES	PER CENT CONTAMINATED
Petroff	59	9	15
Petragagni	54	12	22
Corper-Uyei	59	23	39
Sweany-Evanoff	58	43	74

On the other hand, with Sweany-Evanoff medium, of 58 cultures originally made, 43, or 74 per cent, showed contamination. The latter medium contains no dye. Any attempt to evaluate the relative efficiency of media must needs consider a larger number of tests than were used in this work. However, the findings do indicate that Petroff's is superior to Petragagni's and the latter is superior to Corper's medium. The Sweany-Evanoff medium in this work was practically useless.

CONTROLS

A series of controls, using environments apparently free of tubercle bacilli—such as a dormitory in a fire station and several business offices—was also sampled. The technique of collection and subsequent treatment was identical with that used above. The results were uniformly negative.

SUMMARY

A simple method of collecting air and dust for the isolation of tubercle bacilli has been tried. The method consists in merely exposing evaporating dishes, containing sterile saline solution, for a period of one week in the environment to be examined. The dust residue is collected, centrifugated, digested, stained, or cultured. The results are overwhelmingly positive. The method makes use of no elaborate equipment. It is simple, expedient and applicable to any environment.

The use of 5 per cent oxalic acid as a digestant serves well, but its efficiency is, in a measure, dependent on the cleanliness of the environment. Along this line further work would be in order.

Culture media containing dyes were found to be more efficient than media without dyes. In this work Petroff's medium, containing crystal violet, 0.01 per cent, was more efficient than either Petragagni's medium, containing aqueous brilliant green, approximately 0.1 per cent, or Corper's medium, containing aqueous crystal violet, approximately 0.001,5 per cent.

The Wells centrifuge, running for 20 minutes, aspirating 1.4 cubic feet of air per minute, is not efficient for the sampling of air for the isolation of tubercle bacilli under the conditions of this study.

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THE AMERICAN REVIEW OF TUBERCULOSIS

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ABSTRACTS OF TUBERCULOSIS

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Infectiousness of Tuberculosis.—There is a certain amount of evidence in favor of the theory that adult tuberculosis is a late manifestation of childhood infection. The disease is apt to break out afresh in a patient who has apparently recovered, and this suggests a relapse due to activation of bacilli already present rather than a new infection, but this cannot be taken as evidence that the body is immune to other bacilli. It seems more reasonable to suppose the frequency of relapse due to massive infection from bacilli already present rather than to bacilli from some outside source. Tuberculosis is not so "catching" as mumps or measles, and there is a difference between the first and subsequent doses. Although it may be agreed that an individual is not likely to acquire tuberculosis from a patient provided there is reasonable cleanliness, and that a mild infection confers some slight protection, it is a dangerous doctrine to deny the infectivity of tuberculosis to an adult or child. Clinical disease is the result of infecting the body with a sufficient number of organisms, the body having enough natural immunity, which is variable, to resist the ordinary dose. The number of bacilli required also varies with the degree of acquired immunity. There is strong evidence that *BCG* definitely increases the resistance of infants to tuberculosis, but only to a slight extent. A positive intracutaneous test is recorded in from 87 to 100 per cent of cases. However, allergy must not be confused with immunity. Tolerance, which protects the individual from toxic symptoms, is another factor which is a result of infection. A mild infection produces a state of allergy in the body in about a fortnight. When the body is allergic, it reacts in the same manner to tubercle bacilli whether already present or introduced from some other patient. A massive infection will produce disease in a tuberculin reactor or nonreactor and the greatest source of infection is always the sputum-positive patient.—*The Infectivity of Tuberculosis, L. S. T. Burrell, J. State Med., June, 1936, xliv, 345.*—(*L. F. B.*)

Clinic for Epidemiological Study.—The Henry Phipps Institute clinic organization is planned to give persons under care all the protection present knowledge and facilities offer and to collect routinely detailed and exact information concerning the origin and spread of tuberculosis in the families of patients attending the Clinic. An area of approximately 7½ square miles surrounding the Institute supplies the patients and in 1920 had a population of 248,889. The population contains a large proportion of persons of Irish, Italian, Jewish and Negro descent. The present study is based on 1,000 families, a large number of which have been followed for a maximum of 8 years. The district has 5 subdivisions, each assigned to a visiting nurse who assists in the clinic with the patients from her district. Each person applying to the clinic receives a serial